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# Iron-Catalysed Hydrogenation and Hydroboration Reactions

Alistair James MacNair



THE UNIVERSITY  
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A thesis submitted for the degree of

Doctor of Philosophy

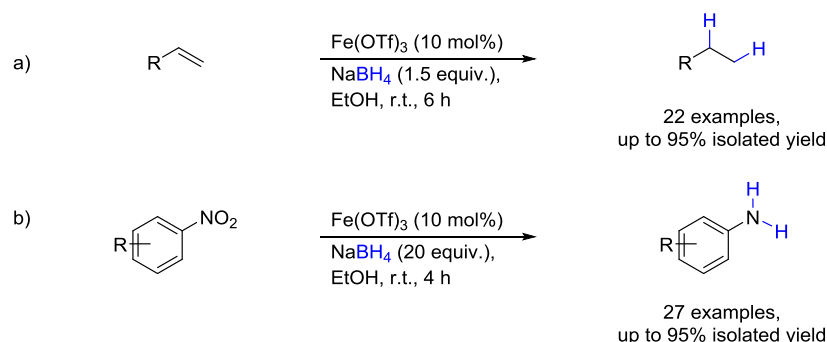
2016



## ABSTRACT

Hydrogenation and hydrofunctionalisation reactions provide efficient, sustainable methodologies for the manipulation of synthetic handles and the formation of carbon-heteroatom bonds from readily available starting materials. Traditional hydrogenation methods typically require precious or semi-precious transition metal complexes or finely divided powders. Iron-based catalysts offer several advantages over more traditional ‘noble’ metal systems due to the high abundance, long-term availability, low cost and low toxicity of iron. To date, the most powerful iron-catalysed hydrogenation and hydrofunctionalisation reactions have required either highly air-sensitive iron(0) complexes or iron(II) complexes activated with an extremely reactive, pyrophoric organometallic reagent.

An operationally simple and environmentally benign formal hydrogenation protocol has been developed using a simple iron(III) salt and NaBH<sub>4</sub>; an inexpensive, bench stable, stoichiometric reductant. This reaction has been applied to the reduction of terminal alkenes (22 examples, up to 95% yield) and nitro groups (26 examples, up to 95% yield) in ethanol, under ambient conditions (Scheme A1).

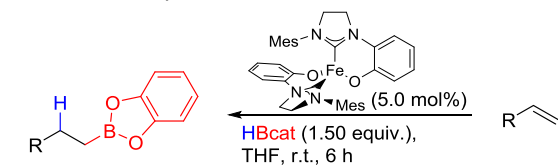


*Scheme A1 Operationally simple, environmentally benign, iron-catalysed formal hydrogenations of  
a) terminal alkenes and b) nitroarenes*

Two novel series of structurally related alkoxy-tethered N-heterocyclic carbene (NHC) iron(II) complexes have been developed as catalysts for the regioselective hydroboration of alkenes. Significantly, Markovnikov selective alkene hydroboration with pinacolborane (HBpin) has been controllably achieved for the first time using an iron catalyst (11 examples, 35-90% isolated yield) with up to 37:1 branched:linear selectivity (Scheme A2). *anti*-Markovnikov selective alkene hydroboration was also achieved using catecholborane (HBcat) and modification of the ligand backbone (6 examples, 44-71% yield). In both cases, ligand design has enabled activator-free iron catalysis.

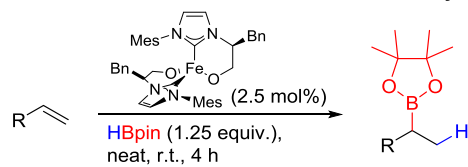


conventional regioselectivity  
for iron catalysis:



6 examples,  
up to 71% isolated yield

novel regioselectivity  
for iron catalysis:



11 examples,  
up to 90% isolated yield  
up to 37:1 branched:linear selectivity

*Scheme A2 Novel alkoxy-tethered NHC iron(II) complexes as catalysts for alkene hydroboration with controlled switchable regioselectivity*

## LAY SUMMARY

The development of catalytic methods for the controlled synthesis of organic molecules was one of the most significant scientific advances of the 20<sup>th</sup> century. The production of vast quantities and diversity of chemical products such as: fertilisers, petrochemicals, polymers and pharmaceuticals has allowed people to live in prosperity unimaginable to previous generations. However, in light of increased worldwide concern regarding sustainability, much modern research focuses on the development of ‘green’ chemical processes.

Iron is one of the most abundant elements on Earth and therefore the use of iron-based species offers many advantages for future ‘green’ catalysts. However, to-date, the development of iron-catalysis has been hindered by a lack operational simplicity, which limits its use to strictly-controlled laboratory conditions.

The work contained herein details the development of novel iron-catalysed reactions for the controlled synthesis of various organic products. These reactions have been developed with the aim of providing reactions that can be performed by chemists who are non-experts in iron-catalysis and providing new methods of producing active iron-catalysts.



# DECLARATION

I certify:

- a) that the thesis has been composed by the student, and
- b) either that the work is the student's own, or, if the student has been a member of a research group, that the student has made a substantial contribution to the work, such contribution being clearly indicated, and
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A handwritten signature in black ink, appearing to read 'A. MacNair', is written on a light blue rectangular background.

Alistair James MacNair, 22<sup>nd</sup> May 2017



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# TABLE OF CONTENTS

Abstract .....	i
Lay Summary .....	iii
Declaration.....	v
Acknowledgements .....	vii
Table of Contents .....	ix
List of Abbreviations .....	xv
Chapter 1. Introduction and Background.....	1
1.1    Preamble .....	1
1.2    Background to Catalysis and Green Chemistry.....	1
1.2.1    Background to Iron Catalysis.....	2
1.2.1.1    Why Choose Iron?.....	2
1.2.1.2    The Prior Art.....	4
1.2.2    Introduction to Organometallic Catalysis.....	5
1.2.3    Organometallic Catalysis for Alkene and Alkyne Hydrogenation and Hydrofunctionalisation.....	9
1.2.3.1    Introduction to Alkene and Alkyne Hydrogenation and Hydrofunctionalisation Reactions.....	9
1.2.3.2    Strategies for Iron-Catalysed Hydrogenation and Hydrofunctionalisation of Alkenes and Alkynes .....	10
1.2.3.3    Accessing Low Oxidation-State Iron Species for Hydrogenation and Hydrofunctionalisation of Alkenes and Alkynes .....	12
1.3    General Aims .....	16
Chapter 2. Operationally Simple, Formal Hydrogenation of Alkenes using Fe(OTf) <sub>3</sub> and NaBH <sub>4</sub> .....	19
2.1    Preamble .....	19
2.2    Introduction .....	19
2.2.1    Alkene and Alkyne Reduction: General Background .....	19
2.2.2    Recent Developments in Iron-Catalysed Alkene and Alkyne Reductions .....	21



2.2.2.1	Pre-Catalysts Bearing Activating Groups for Alkene and Alkyne Hydrogenation .....	21
2.2.2.2	Low Oxidation-State Iron Pre-Catalysts for Alkene and Alkyne Hydrogenation .....	24
2.2.2.3	<i>In Situ</i> Activation of High Oxidation-State Iron Pre-Catalysts for Alkene and Alkyne Hydrogenation.....	31
2.2.2.4	Nanoparticulate Iron-Catalysts for Alkene and Alkyne Hydrogenation .....	35
2.2.2.5	Iron-Catalysed Alkene and Alkyne Formal Hydrogenations .....	42
2.3	Project Aims .....	47
2.4	Results and Discussion.....	49
2.4.1	Catalyst Identification .....	49
2.4.1.1	Preliminary Work .....	49
2.4.1.2	Methodology Development.....	51
2.4.2	Control Reactions.....	56
2.4.3	Substrate Scope.....	58
2.4.4	Mechanistic Investigations .....	65
2.4.4.1	Investigations into Radical Intermediates .....	65
2.4.4.2	Deuterium Labelling Reactions.....	66
2.5	Conclusions.....	68
Chapter 3. Operationally Simple, Formal Hydrogenation of Nitro Groups using Fe(OTf) <sub>3</sub> and NaBH <sub>4</sub> .....		71
3.1	Preamble.....	71
3.2	Introduction.....	71
3.2.1	Nitro group Reduction: General Background .....	71
3.2.2	Recent Developments in Iron-Catalysed Nitro Group Reductions.....	73
3.2.2.1	Iron-Carbonyl Species as Hydrogenation Catalysts.....	73
3.2.2.2	Iron-Catalysed Nitro Group Hydrogenation Reactions .....	74
3.2.2.3	Iron-Catalysed Transfer Hydrogenations of Nitro Groups .....	76
3.2.2.4	Iron-Catalysed Formal Hydrogenations of Nitro Groups .....	77

3.3	Project Aims.....	82
3.4	Results and Discussion.....	83
3.4.1	Catalyst Identification and Methodology Development .....	83
3.4.2	Substrate Scope .....	84
3.5	Conclusions .....	88
Chapter 4. Iron-Catalysed Alkene Hydroboration Reactions.....		89
4.1	Preamble .....	89
4.2	Introduction .....	89
4.2.1	Organoboranes in Organic Chemistry .....	89
4.2.2	Synthesis of Organoboranes .....	91
4.2.3	Alkene and Alkyne Hydroboration: General Background.....	92
4.2.3.1	Early Work.....	92
4.2.3.2	Hydroboration Reactions Under Catalytic Control .....	95
4.2.3.3	Recent Developments in Metal-Catalysed Hydroboration Reactions.....	99
4.2.3.4	Iron-Catalysed Alkene Hydroboration Reactions .....	100
4.2.3.5	Iron-Catalysed Diene Hydroboration Reactions .....	107
4.2.3.6	Iron-Catalysed Alkyne Hydroboration Reactions .....	109
4.2.4	Non-Innocent Ligands in Iron Catalysis.....	110
4.3	Project Aims.....	113
4.4	Results and Discussion.....	115
4.4.1	Synthesis of Alkoxy-Tethered <i>N</i> -Heterocyclic Carbene Iron(II) Complexes.....	115
4.4.1.1	Synthesis of Aryloxy-Tethered Imidazolinium Salts.....	115
4.4.1.2	Synthesis of Alkoxy-Tethered Imidazolium Salts.....	117
4.4.1.3	Synthesis of Novel Iron(II) NHC Complexes.....	118
4.4.2	Preliminary Assessment of Catalytic Activity.....	122
4.4.3	Development of Iron(II)-Catalysed Hydroborations Using Catecholborane.....	124
4.4.3.1	Methodology Development.....	124
4.4.3.2	Substrate scope .....	127

4.4.4	Development of Iron(II) Catalysed Hydroborations Using Pinacolborane .....	129
4.4.4.1	Methodology Development.....	129
4.4.4.2	Substrate Scope.....	136
4.4.5	Mechanistic Investigations .....	138
4.4.5.1	Deuterium Labelling Experiments .....	138
4.4.5.2	Radical Inhibition Experiments .....	139
4.4.5.3	Reaction Monitoring by <i>In Situ</i> ESI-MS .....	140
4.5	Conclusions and Future Work.....	143
Chapter 5: Experimental .....		145
5.1	General Experimental .....	145
5.2	Preparation of Alkene Derivatives .....	147
5.3	Alkene Hydrogenation with NaBH <sub>4</sub> : Reaction Optimisation.....	150
5.4	Alkene Hydrogenation with NaBH <sub>4</sub> : Isolated Products.....	152
5.5	Alkene Hydrogenation with NaBH <sub>4</sub> : Deuterium Labelling Experiments .....	160
5.6	Nitro Group Hydrogenation Reactions with NaBH <sub>4</sub> : Reaction Optimisation.....	163
5.7	Nitro Group Hydrogenation with NaBH <sub>4</sub> : Isolated Products .....	163
5.8	Imidazolinium Salt Synthesis.....	176
5.9	Imidazolium Salt Synthesis.....	184
5.10	Iron <i>N</i> -Heterocyclic Carbene Complex Syntheses.....	189
5.11	Hydroboration Reactions with Catecholborane: Reaction Monitoring by NMR Spectroscopy.....	192
5.12	Hydroboration Reactions with Catecholborane: Isolated Products .....	196
5.13	Hydroboration Reactions with Pinacolborane: Reaction Optimisation.....	202
5.14	Hydroboration Reactions with Pinacolborane: Reaction Monitoring by NMR Spectroscopy.....	203
5.15	Hydroboration Reactions with Pinacolborane: Isolated Products.....	206
5.16	Hydroboration Reactions with Pinacolborane: Deuterium Labelling Experiments ..	215
5.17	Hydroboration Reactions: Reaction Monitoring with ESI-MS .....	218
5.18	X-Ray Crystallography Data (Summary) .....	230

References.....	231
Appendix 1: Publications.....	245
Appendix 2: NMR Spectra.....	246
Appendix 3: X-Ray Crystallographic Data .....	246



## LIST OF ABBREVIATIONS

2-MeTHF	-	2-methyltetrahydrofuran
9-BBN	-	9-borabicyclo[3.3.1]nonane
Ac	-	acetyl
acac	-	acetylacetonate
Ar	-	aryl
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIP	-	bis(imino)pyridine
BIPY	-	2,2'-bipyridine
bMepi	-	<i>N,N,N</i> -1,3-bis(6'-methyl-2'-pyridylimino)isoindolate
Bn	-	benzyl
cat	-	catecholate
CDG	-	chemically derived graphene
COD	-	cyclooctadiene
Cp*	-	pentamethylcyclopentadienyl
CSNP	-	core-shell nanoparticle
Cy	-	cyclohexyl
dba	-	dibenzylideneacetone
DCT	-	dibenzo[ <i>a,e</i> ]cycloocta-tetraene
DFT	-	density functional theory
diglyme	-	1-methoxy-2-(2-methoxyethoxy)ethane
Dipp	-	2,6-diisopropylphenyl
DME	-	dimethoxyethane

DMF	-	<i>N,N</i> -dimethylformamide
E°	-	standard electrode potential
EDX	-	energy-dispersive X-ray spectroscopy
EDTA	-	ethylenediaminetetraacetate
EI	-	electron impact
EPR	-	electron paramagnetic resonance
equiv.	-	equivalents
ESI	-	electrospray ionisation
EXAFS	-	extended X-ray absorption fine structure
GCMS	-	gas chromatography mass spectroscopy
HPLC	-	high pressure liquid chromatography
ICP-MS	-	inductively coupled plasma mass spectroscopy
IMes	-	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IP	-	iminopyridine
IPO	-	iminopyridine oxazoline
IPr	-	1,3-bis(2,6-diisopropylphenyl)-imidazolium
IR	-	infrared
L	-	ligand
M	-	metal
Mes	-	2,4,6-trimethylphenyl
MOF	-	metal organic framework
NADPH	-	nicotinamide adenine dinucleotide phosphate hydride
NHC	-	<i>N</i> -heterocyclic carbene
NMP	-	<i>N</i> -methyl-2-pyrrolidone

NMR	-	nuclear magnetic resonance
PDI	-	bis(diisopropylphosphino)pyridine
PEG	-	polyethylene glycol
pin	-	pinacolate
ppm	-	parts per million
py	-	pyridine
R	-	alkyl
R <sub>f</sub>	-	retention factor
ROP	-	ring opening polymerisation
sal	-	salicylate
TBAF	-	tetrabutylammonium acetate
TBDMS	-	<i>tert</i> -butyl dimethylsilyl
TEM	-	transmission electron microscopy
TEMDA	-	<i>N,N,N',N'</i> -tetramethylethane-1,2-diamine
TEMPO	-	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TERPY	-	2,6-bis(2-pyridyl)pyridine
Tf	-	trifluoromethanesulfonate
TFA	-	trifluoroacetic acid
tpp	-	tetraphenylporphyrinato
Ts	-	<i>para</i> -tolylsulphonate
THF	-	tetrahydrofuran
TMDB	-	4,4,6-trimethyl-1,3,2-dioxaborinane
STEM	-	scanning transmission electron microscopy
SQUID	-	superconducting quantum interference device



UV	-	ultraviolet
XANES	-	X-ray absorption near edge structure
XAS	-	X-ray absorption spectroscopy
XPS	-	X-ray photoelectron spectroscopy

# CHAPTER 1. INTRODUCTION AND BACKGROUND

## 1.1 PREAMBLE

Chapter 1 consists of an introduction to this document, intending to place the research presented in later chapters in the appropriate context. Firstly the use of Earth-abundant metal catalysis, particularly with iron, in the context of the development of environmentally benign ‘green’ chemistry is presented, along with a discussion of organometallic catalysis in general. A discussion of alkene and alkyne hydrogenation and hydrofunctionalisation reactions is presented along the strategies used to achieve these reactions using iron catalysis. Finally the general aims guiding the research presented in this thesis are given.

## 1.2 BACKGROUND TO CATALYSIS AND GREEN CHEMISTRY

The study of catalysis is of enormous importance in the fields of biochemistry, bulk and fine chemical synthesis and environmental chemistry. Catalysts are chemical species that lower the activation energy required to perform a reaction between other chemical species while themselves being returned unchanged from a reaction.

The whole of life is only possible due to a huge range of biological catalysts that assist in the transformation of inert chemicals into the enormous wealth of biodiversity present in the world around us. Man-made catalysts have not yet achieved the diversity and complexity of their biological counterparts, but their development has, over the course of the last century, enabled many of the aspects of what we consider to be the ‘modern world’ to be produced.<sup>1</sup> The bulk chemical industry produces petro-chemicals and fertilisers inexpensively and in vast quantity and diversity, supporting a global population expansion from 1.6 billion in 1900 to over 7 billion today.<sup>2</sup> It is not just in chemical synthesis that catalysts have a critical role to play. In devices such as catalytic converters on cars, catalysts allow all manner of waste disposal and environmental remediation.

The ‘fine’ chemical industry, which produces specific products of high purity, has also been one of the major transforming worldwide influences, producing all manner of pharmaceutical products, polymers, fuels and agrochemicals among a great many others. However, this abundance of end-products has not always been associated with sustainability of either feedstocks or processes. From the poisoning of workers in tetraethyl lead factories in the 1920s,<sup>3</sup> to the chronic shortages of Tamiflu in the early 2000’s due to reliance on the Chinese Star Anise harvest,<sup>4</sup> sustainability has been a constant limitation for the chemical industry.

In recent years a great deal of effort, by chemical companies and academic institutions, has focused on improving the sustainability and environmental impact of the chemical industry.

These ideas are often described as a ‘green chemistry paradigm’.<sup>5,6</sup> While the specific priorities of academic researchers and those in industry may often vary, the general criterion of sustainability is increasingly universal.<sup>7</sup>

Key ideas of this paradigm are the use of sustainable and non-toxic reagents and solvents, a low number of steps in syntheses, high atom economy reactions,<sup>8</sup> and the use of catalysis in order to lower the energy cost of reactions. Since catalysts lower the activation energy of reactions, they often allow reactions to proceed under ambient temperatures and pressures that would otherwise require considerable energy input.

## **1.2.1 BACKGROUND TO IRON CATALYSIS**

### **1.2.1.1 Why Choose Iron?**

In the bulk chemical industry, heterogeneous iron-catalysts have been exploited since the early twentieth century on an enormous scale, in processes such as the Haber-Bosch ammonia synthesis,<sup>9</sup> and the Fischer-Tropsch hydrocarbon synthesis.<sup>10</sup> However, particularly in the fine chemical industry, catalyst development has been dominated by systems based on precious metals such as platinum, palladium, iridium, rhodium and ruthenium. These ‘noble’ metal systems have resulted in a huge range of robust catalytic processes with excellent chemo-, regio- and stereo- selectivity.<sup>11</sup>

For the noble metals, it has been a case of success breeding further success: the ubiquity of precious metal-catalysed processes has led to an abundance of both commercially available catalytic precursors and the knowledge and understanding required to use them, facilitating further development of related systems.<sup>12</sup> Additionally, precious metals often form stable and synthetically tractable complexes, greatly facilitating the use of combinatorial chemistry for the development of new systems.<sup>13,14</sup> The importance of precious metal catalysis to the development of synthetic organic chemistry has led to recognition at the highest level.<sup>15–17</sup>

Despite the undeniable success of precious metal systems, and their contributions to ‘green’ chemistry, it must be admitted that they are based on strictly limited resources.<sup>18</sup> Precious metals are inherently not Earth-abundant, therefore the use of them must be considered in the light of the considerable issues regarding sustainability.

Platinum group metals are mined from only a handful of sources, and stockpiles of noble metals are typically controlled by the handful of major producers leading to price volatility and a lack of supply security.<sup>19</sup> South Africa produces 80% of the world’s platinum, and Russia and South Africa between them produce 84% of the world’s palladium. Production of platinum group metals has also declined 23% between 2010 and 2014.<sup>20</sup> In addition to long-term sustainability

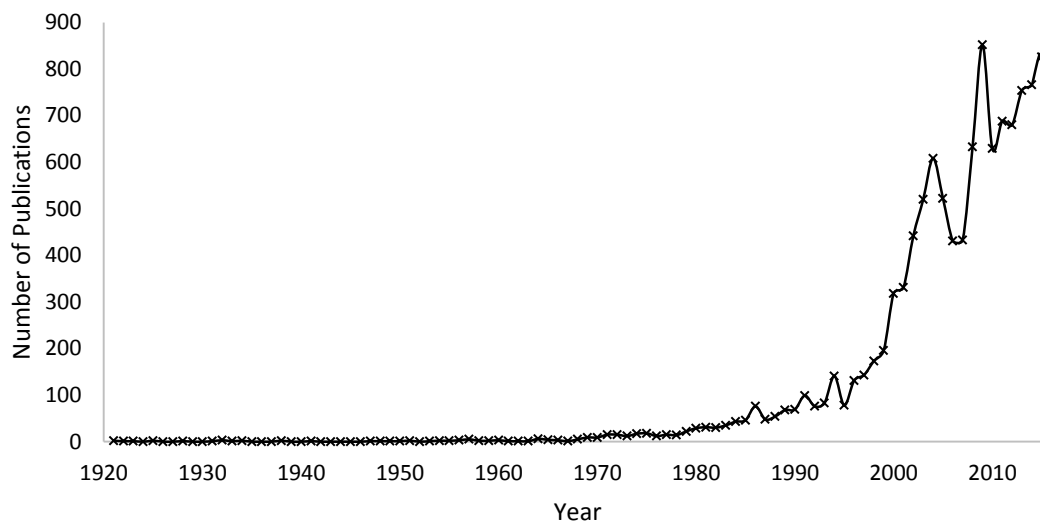
issues the short-term environmental,<sup>21</sup> and human cost of mining low grade deposits of precious metals can be considerable.<sup>22</sup>

Due to these limitations in the existing catalyst paradigms, in recent years a great many researchers have taken to developing catalytic systems based on the much more abundant first row transition metals such as manganese, cobalt, nickel, copper, zinc and iron. In terms of 'green chemistry', iron has particular advantages due to representing 32% of the mass of the Earth.<sup>23</sup> Iron is the 4<sup>th</sup> most abundant element, and the most abundant metal, in the Earth's crust representing 4.7% of its mass. Thanks to this very high abundance iron species are very inexpensive, and the price is considerably less volatile than that of many noble metals. Additionally, iron species are generally environmentally benign and show low toxicity. For example, the residual metal traces allowed in active pharmaceutical ingredients are two orders of magnitude greater for iron than those allowed for precious metals such as platinum, palladium, iridium, rhodium and ruthenium, or other Earth-abundant metals such as nickel and cobalt.<sup>24–27</sup> However it should be noted that while iron is unquestionably a sustainable metal, metal-toxicity is difficult to generalise and depends on factors such as bioavailability, solubility, oxidation-state, particle size and ligand effects.<sup>28</sup>

Beyond the field of 'green' chemistry, the development of entirely novel catalytic methods is of great interest due to the possibilities for new modes of reactivity and selectivity.<sup>29</sup> Iron has extremely rich redox and Lewis acid chemistry,<sup>30</sup> and iron complexes are widely used in biological systems,<sup>31</sup> offering the potential for development of biomimetic catalysts. However, in spite of these advantages iron based catalysts have been relatively poorly developed, and the general level of understanding required for widespread adoption of iron catalysts has not yet been realised.

### 1.2.1.2 The Prior Art

Over the last decade or so, interest in iron-catalysis for fine chemical synthesis has increased, and the number of publications relating to iron-catalysis has rapidly increased in recent years (Figure 1.01).<sup>32</sup>



**Figure 1.01** Scopus search for papers bearing the keywords 'iron catalysis', retrieved 15/09/2016.

Cross-coupling reactions between organic electrophiles and (typically) organometallic nucleophiles, are probably the most thoroughly investigated class of iron-catalysed reactions and comprise a significant fraction of the existing literature.

Iron-catalysed cross-coupling of Grignard reagents and alkenyl-halide reagents, typically known as the Kumada coupling reaction, was reported by the group of Kharasch in the 1940s,<sup>33,34</sup> and by Kochi in the 1970s,<sup>35,36</sup> before the topic was eclipsed by the aforementioned ubiquity of precious metal catalysed cross-couplings.

As part of the general trend toward more sustainable chemistry, the field of iron-catalysed Kumada couplings has been subject to a great deal of research in recent years.<sup>37</sup> This has resulted in a good empirical understanding of the reaction and development of several sets of effective reaction conditions.<sup>38–40</sup> The cross-coupling of  $C(sp^3)$  Grignard reagents with a wide range of  $C(sp^2)$  and  $C(sp^3)$  electrophiles has been achieved. Significantly, this allows access to  $C(sp^3)$ - $C(sp^3)$  cross-coupling reactions, a reaction that precious metal catalysts have traditionally struggled to perform.<sup>41,42</sup> Iron-catalysed Kumada coupling reactions have been exploited for industrial syntheses,<sup>43–45</sup> however theoretical understanding of the reaction mechanisms and the nature of the catalytically active species remains widely disputed in the literature.<sup>46–48</sup>

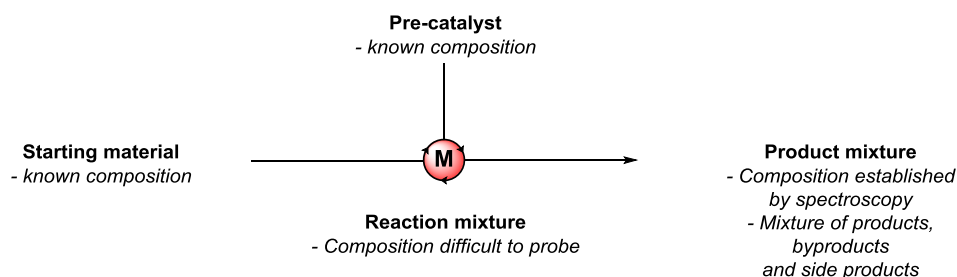
Iron-catalysed cross-coupling reactions generally limited to Grignard reagents, limiting the tolerance of the reaction towards air, moisture and acidic or electrophilic functional groups. Despite some early set-backs involving several retraction notices<sup>49–53</sup> more recent work has even developed iron-catalysed formal Suzuki-Miyaura coupling reactions,<sup>54–61</sup> by the generation of boronate complexes.<sup>62</sup>

Additionally, the number of transformations catalysed by iron has expanded dramatically,<sup>63–65</sup> and now includes, but is not limited to, hydrogenation,<sup>66–68</sup> hydrofunctionalisation,<sup>67</sup> oxidation,<sup>69,70</sup> and epoxidation reactions,<sup>71</sup> and includes limited examples of asymmetric syntheses.<sup>72,73</sup>

### 1.2.2 INTRODUCTION TO ORGANOMETALLIC CATALYSIS.

The research presented below largely concerns iron-catalysed reactions under reductive conditions. Therefore a general discussion regarding metal catalysts and catalytic reactions under redox-active conditions should be made. Other systems, such as enzymatic catalysts or organocatalysts are outside the scope of this document, and will not be discussed.

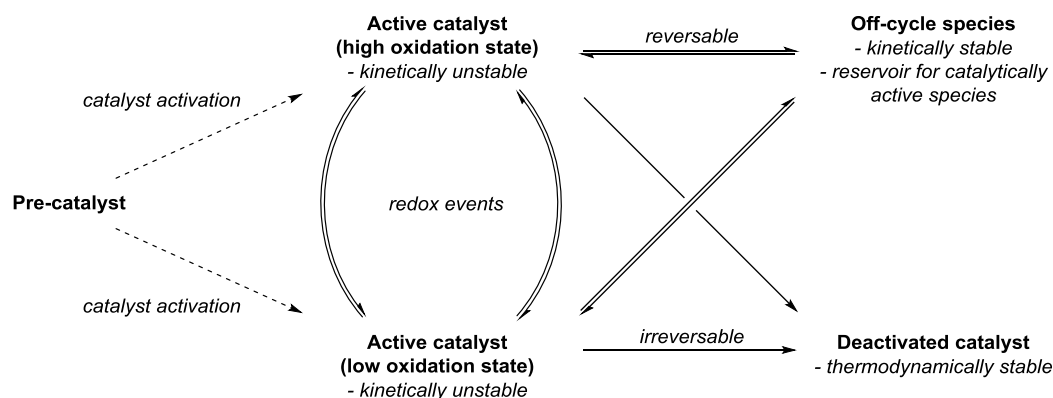
In any catalytic system starting materials and a pre-catalyst, both typically of known composition, are added to a system, which undergoes some form of catalytic cycle, producing a mixture of products whose composition can be probed by standard spectroscopic techniques (Scheme 1.01). While the organic components of a reaction mixture can be monitored by time-course spectroscopy, the transient nature of catalytic intermediates can make them difficult to study under conventional conditions.



**Scheme 1.01** General scheme to illustrate a catalytic process.

The pre-catalyst species will typically undergo some form of catalyst activation to form a species on the catalytic cycle (Scheme 1.02). The resulting ‘active’ species may proceed through the catalytic cycle, often undergoing redox processes, consuming starting materials and generating products. At any given point on a catalytic cycle, the on-cycle active species can potentially undergo transformation to off-cycle species. This transformation may be reversible, leading to reservoirs of off-cycle or ‘resting state’ species, or irreversible leading to deactivation of the

catalyst.<sup>48</sup> The terms ‘activation’ and ‘deactivation’ are rather nebulous and can refer to numerous processes including, but not limited to: de-ligation; ligand exchange; redox events; agglomeration, removal of oxides and solvation.



**Scheme 1.02** General scheme to illustrate the groups of species that can be formed from a given pre-catalyst in redox-active catalytic reactions.

This description of a generic catalytic cycle, while simplistic, illustrates several important points. Firstly, while the initial composition of the pre-catalyst is generally known, the structure and oxidation-state of the pre-catalyst does not necessarily bear any resemblance to those of the catalytically active species.<sup>48</sup> Secondly, in any given reaction mixture a whole ensemble of species derived from the pre-catalyst may be present, and the ‘active’ species may only represent a small fraction of the pre-catalyst material. Therefore, simply because a metal complex is observed in a reaction mixture does not mean that it is catalytically relevant. Additionally, that a structure is thermodynamically stable enough to be isolated from a reaction mixture, could imply that it is not kinetically unstable enough to be an ‘active’ species and may represent a ‘resting-state’ species rather than a transiently stable catalytic intermediate.

Traditionally, metal catalysts were categorised into two major groups: heterogeneous catalysts, which are in a different phase to the reactants; and homogeneous catalysts, which are in the same phase as the reactants.

Heterogeneous systems, most typically, use solid pre-catalysts, either of a single catalytic species or of a catalyst immobilised on to a chemically inert solid support, that promote reactions between substrates in a fluid phase.<sup>74</sup> Reactions then proceed at active sites on the solid surfaces of the catalytic species, often features such as corners, facets or steps. Typically, this requires one or more of the substrates to be adsorbed on to the surface of the catalyst prior to reactions occurring, a step which is often rate limiting. Due to the separate catalyst and substrate phases, heterogeneous catalysts are often extremely easy to separate, or recover, from reaction mixtures by techniques such as filtration or washing. The development of heterogeneous catalysis is often

a highly empirical process, which proceeds by the use of various additives and poisons, along with modification of preparation methods to change the nature of active sites.

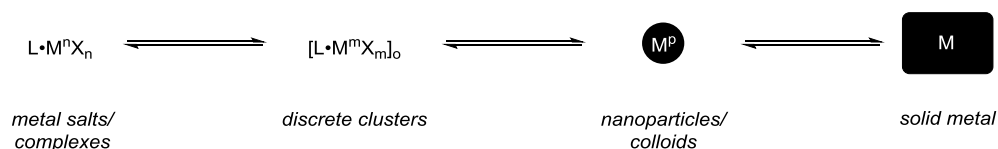
Homogeneous systems typically use soluble metal pre-catalyst species which provide discrete active complexes, stabilised by some kind of ligand(s), in solution that promote reactions between substrates in a fluid phase.<sup>75</sup> Homogeneous catalysts are usually generalised as having a much higher effective proportion of active sites for a given loading of metal. Thus they have been shown to often have superior activity and selectivity compared to heterogeneous examples. However, this superior reactivity can be offset by being much harder to separate from the reaction mixtures. Homogeneous systems can be highly tuneable by modification of structure of the complex, typically by tuning the nature of the ligands and the identity of the metal centres.

In recent years, it has become apparent that this simple view of discrete catalytic manifolds does not adequately represent the messy reality of many organometallic catalytic systems.<sup>76</sup>

Firstly, many groups have reported the synthesis and use of isolated and characterised nanoparticulate and colloidal metal species as catalysts for a wide range of reactions.<sup>77,78</sup> These species exist at the border of the homogeneous and heterogeneous regimes and offer the possibility of very high surface areas compared to traditional heterogeneous catalysts while often being more easily recovered than homogenous catalysts. The reactivity of nanoparticles is tuned by properties such as: size; crystallinity; the nature of exposed facets; dispersity; composition; and the nature of any ligands or surfactants present.

Heterogeneous pre-catalysts have been reported to generate catalytically active soluble species following leaching of the metals into solution.<sup>79</sup> Additionally, heterogeneous, colloidal and nanoparticulate species have been generated *in situ* from homogeneous pre-catalysts and can act as both on-cycle active species in their own right, as off-cycle species and reservoirs of the active catalyst, or simply as inert spectators.<sup>80</sup> It has been shown, therefore, that in certain catalytic systems rather than there being a single homogeneous or heterogeneous catalytic species, there is a continuum of species that can conceivably be accessed, or that can mature from a given pre-catalyst. These range from discrete complexes, to small clusters, nanoparticles of various sizes, continuous colloids and solid metal species (Scheme 1.03). Any one of these metal species, or an ensemble thereof, may be present in a reaction mixture and a given reaction may be catalysed by a single species from a mixture or by several species acting in similar catalytic cycles.<sup>81</sup> Control over the formation of particles and heterogeneous species in solution can be achieved by the appropriate use of pre-catalysts and ligands.





**Scheme 1.03** Continuum of species accessible in a given reaction mixture depending on conditions and ligands present.

This understanding of the potential complexity of catalytic systems has led to the development of newer definitions of catalyst manifolds: heterotopic catalysts that have more than one active site and homotopic catalysts, which have a single kind of active site.<sup>82,83</sup> Heterotopic systems typically have irregular structures, leading to an ensemble of active sites available for catalysis, and would include heterogeneous catalysts such as Pd/C and some homogeneous (soluble) nanoparticulate systems. Homotopic systems generally generate molecularly well-defined active catalytic species, with a single (or small number) of active sites, and includes homogeneous species such as soluble well-defined nanoclusters and heterogeneous species such as complexes immobilised on to solid supports.

Numerous diagnostic tests for the *in situ* formation heterogeneous species from homogeneous pre-catalysts are suggested in the literature, typically: the use of Hg(0) to sequester low oxidation-state particles; selective poisoning experiments with *P*-donor ligands; and hot filtration tests. It should be noted however that accurately determining the active catalytic manifold for a newly developed reaction can be extremely difficult and these tests are most successful when used as part of a systematic investigation of the kinetics of the reactions and of catalyst activation. The consequence of this is that accurately determining the mechanism by which a given catalytic reaction proceeds is often a lengthy, systematic and time-consuming process, and often lags behind the relatively empirical research to develop novel catalytic systems.

It should also be noted that the majority of research performed on these kinds of borderline homogeneous/heterogeneous systems has been performed on systems using precious metal catalysts. The use of iron catalysts presents several unique challenges since the typical ‘diagnostic’ tests for homogeneity or nanoparticle formation are often even less efficient when used with iron species than with precious metals: iron does not readily form stable amalgams with mercury,<sup>84,85</sup> the use of phosphine ligands as poisons have generally been reported to be inconclusive;<sup>86</sup> and many of the reported Fe<sup>0</sup> nanoparticles are tiny ( $\leq 5$  nm) making even filtration problematic (*vide infra*). Additionally since many iron species are paramagnetic the use of various spectroscopic techniques, particularly NMR techniques, can be impractical. This can make studying the kinetics of the reaction also difficult. However, systematic analysis of iron-based catalytic systems is not impossible, and has been achieved, for example using techniques

such as: Mössbauer spectroscopy;<sup>87,88</sup> X-ray absorption spectroscopy (XAS);<sup>89</sup> and reaction kinetics and poisoning reactions with reagents such as dibenzo[*a,e*]cycloocta-tetraene (DCT).<sup>81</sup>

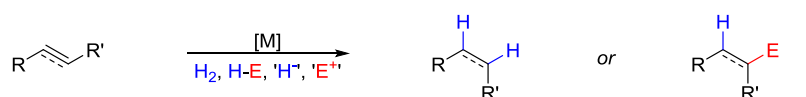
It is often most expedient, therefore, to categorise reactions by the nature of the pre-catalyst, and the pre-catalyst activation. Additionally, these factors are of critical importance since a reaction typically needs either to be of extreme interest or utility to attain widespread adoption in academia or industry and therefore warrant the investment of the considerable time and effort required for significant mechanistic understanding.

In designing an 'ideal' catalytic system then, pre-catalysts and reagents need to be widely available, easily handled and sustainable to acquire and dispose of. An 'ideal' pre-catalyst should be relatively inert, except to the designed activation process and in order to minimise the requirement of catalyst loading, the pre-catalyst should be cleanly converted to the active species in high yield, which should be both resilient towards deactivation (or readily re-activated) and highly reactive with substrate.

### **1.2.3 ORGANOMETALLIC CATALYSIS FOR ALKENE AND ALKYNE HYDROGENATION AND HYDROFUNCTIONALISATION**

#### **1.2.3.1 Introduction to Alkene and Alkyne Hydrogenation and Hydrofunctionalisation Reactions**

Simple alkenes are a class of reagents that are extremely common and inexpensive due to their ubiquity in the polymer industry and as such they are valuable feedstock reagents for a wide variety of reactions. Since C-C multiple bonds are relatively inert to many reaction conditions, alkenes and alkynes can often be carried through syntheses intact and without protecting groups. Thus, reactions that can selectively modify or functionalise C-C double bonds are valuable since they allow the transformation of simple, stable, inexpensive synthetic handles into value-added products and also offer the possibility of substrate functionalisation at a late stage of synthesis. Much of the work contained in this document consists of metal-catalysed hydrogenation and hydrofunctionalisation of alkenes and alkynes, with specific focus on hydrogenation and hydroboration. These reactions are conceptually, and often mechanistically, linked by both being additions of H and another element across a C-C multiple bond (Scheme 1.04).<sup>90</sup>



Examples include:

<b>E = H,</b>	hydrogenation
<b>Si,</b>	hydrosilylation
<b>B,</b>	hydroboration
<b>M,</b>	hydrometallation
<b>CO,</b>	hydroformylation
<b>CN,</b>	hydrocyanation

**Scheme 1.04** Metal-catalysed hydrogenation and hydrofunctionalisation of alkenes and alkynes

There are myriad powerful precious-metal catalysed hydrogenation systems, which are widely used in both: the bulk chemical industry, for example food processing,<sup>91</sup> and in fine-chemical industrial applications.<sup>92–94</sup> For example, the GlaxoSmithKline reagent guide for green alkene reduction suggests 22 systems to be used in initial reactivity investigations. Of these 22 examples of ‘stereotypical’ alkene reductions, 15 are catalytic systems for hydrogenation or formal hydrogenation and 14 of those utilise precious metal catalysts.<sup>95</sup> The most common systems for alkene hydrogenation use heterogeneous pre-catalysts:<sup>96</sup> palladium nanoparticles supported on activated carbon (Pd/C) or platinum metal and its oxides.<sup>97</sup> Catalyst poisons are regularly used to moderate the reactivity of complexes, for example allowing the semi-hydrogenation of alkynes to alkenes using Lindlar’s catalyst.<sup>98</sup>

There are also numerous examples of homogeneous precious metal pre-catalysts, suitable for the hydrogenation of C-C multiple bonds.<sup>99</sup> These range from common commercially available species such as Wilkinson’s catalyst  $[\text{Rh}^{\text{I}}(\text{PPh}_3)_4\text{Cl}]$ ,<sup>100,101</sup> or Crabtree’s catalyst  $[\text{Ir}^{\text{I}}(\text{COD})(\text{PCy}_3)(\text{py})\text{PF}_6]$ ,<sup>102</sup> to highly selective complexes bearing optimised ligands designed to give very well-defined chemo-, regio- and stereoselectivities under specific conditions.<sup>103–106</sup>

In addition to hydrogenation, hydrofunctionalisation reactions represent important industrial and academic uses of precious metal-catalysis. For example, the cross-linking of polymers by hydrosilylation, catalysed by species such as Karstedt’s catalyst  $\{\text{Pt}^0[(\text{Me}_2\text{SiCH}=\text{CH}_2)_2\text{O}]_3\}$ ,<sup>107</sup> represents one of the largest industrial consumers of Pt, despite reactions typically being performed with  $\leq 100$  ppm of catalyst.<sup>108</sup>

### 1.2.3.2 Strategies for Iron-Catalysed Hydrogenation and Hydrofunctionalisation of Alkenes and Alkynes

While iron-catalysed cross-coupling reactions are perhaps the most thoroughly investigated aspect of iron-catalysis, considerable developments have been made in recent years in the field of iron-mediated hydrogenation and hydrofunctionalisation reactions. Specific introductions and

literature reviews are presented in the relevant chapters (*vide infra*), the following sections will attempt to provide a general overview of the topic.

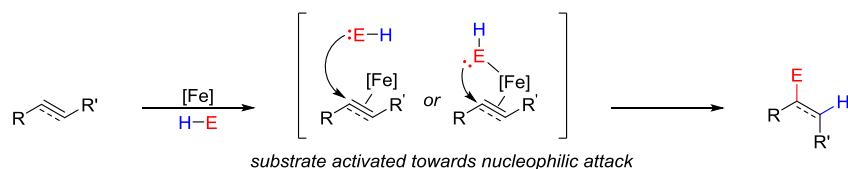
Iron-mediated alkene and alkyne hydrogenation and hydrofunctionalisation reactions can be grouped loosely into three major strategies (Scheme 1.05).<sup>109</sup>

Firstly high oxidation-state iron species have been used as Lewis acids to activate alkenes and alkynes, by coordination, towards attack by nucleophilic reagents (Scheme 1.05 a). These reactions have been proposed to proceed both through inner-sphere and outer-sphere mechanisms, whereby the nucleophile is either coordinated to the catalyst or not, respectively. This system relies on having nucleophilic reagents to attack the activated alkene, and has been used to facilitate the addition of amines, alcohols, carboxylic acids, thiols, 1,3-dicarbonyls, alkenes, alkynes and arenes to alkenes, alkynes and allenes.<sup>109</sup>

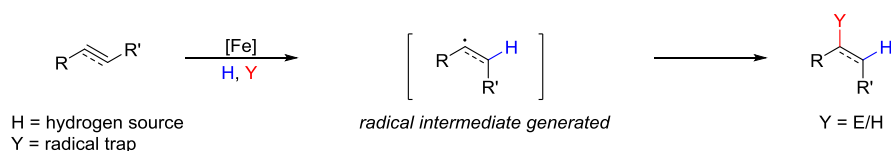
Secondly, there are numerous reports of the use of high oxidation-state iron species, and other first row transition metals species, to mediate the generation of alkyl- radicals from alkenes and alkynes (Scheme 1.05 b).<sup>110–112</sup> For example, stoichiometric iron(III) salts have been demonstrated as active for generating alkyl- radical species, leading to various cyclisation reactions.<sup>113–115</sup> Alternatively, the group of Boger demonstrated that iron(III) salts can be used alongside NaBH<sub>4</sub> to generate alkyl- radicals suitable for the formal hydrogenation,<sup>116</sup> and formal hydrofunctionalisation of alkenes.<sup>117,118</sup> The group of Baran has reported the use of substoichiometric iron(III) salts and silane reagents for the formal hydroalkylation,<sup>119,120</sup> formal hydromethylation,<sup>121</sup> and formal hydroamination of alkenes.<sup>122</sup> This strategy has also been reported for alkene hydroamination.<sup>123</sup>

The third major strategy for the iron-catalysed hydrogenation and hydrofunctionalisation of C-C multiple bonds is the use of low oxidation-state iron species as catalysts (Scheme 1.05 c). The propensity of these low oxidation-state species for undergoing 1- and/or 2-electron redox processes means that this strategy is widely exploited to generate active catalytic systems.

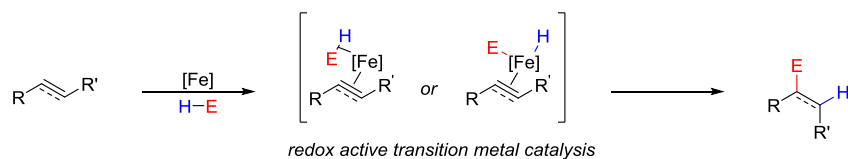
a) High oxidation-state iron species as Lewis acids



b) Iron species as radical mediators



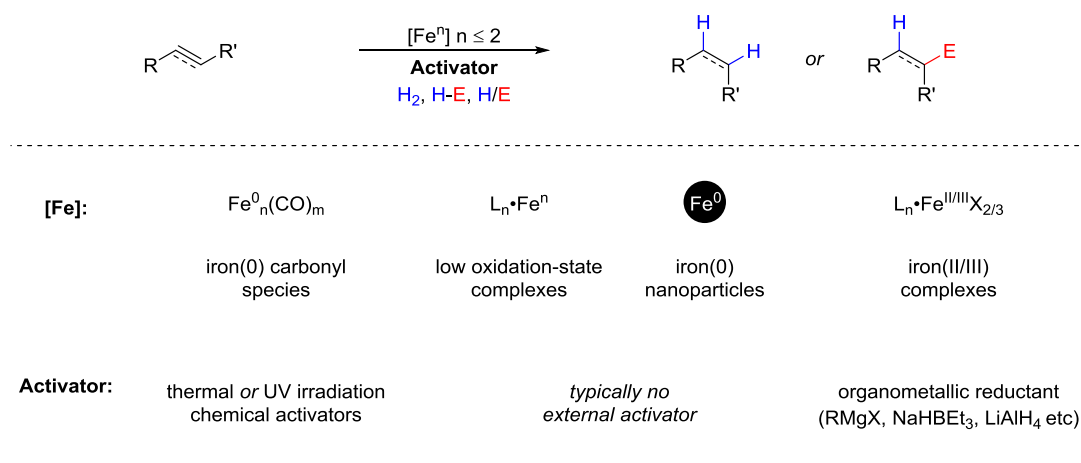
c) Low oxidation-state iron species as redox active catalysts



**Scheme 1.05** General strategies for the iron-catalysed hydrofunctionalisation alkenes and alkynes.<sup>65–68, 109</sup> E = H or heteroatom.

### 1.2.3.3 Accessing Low Oxidation-State Iron Species for Hydrogenation and Hydrofunctionalisation of Alkenes and Alkynes

The significance of low oxidation-state iron-catalysis is such that numerous approaches have been reported to access the active catalytic species. These can be grouped loosely into the following categories, depending on the pre-catalyst and activation strategy used: firstly the use of iron(0) carbonyl species as pre-catalysts; the use of well-defined iron(0) complexes or nanoparticles; and the use of iron(II/III) pre-catalysts, activated *in situ* by a reductant (Scheme 1.06).



**Scheme 1.06** Typical strategies for accessing low oxidation-state iron complexes for alkene hydrogenation and hydrofunctionalisation

Iron(0) carbonyl species are air- and moisture stable low oxidation-state iron pre-catalysts, that have been known for over 100 years and have been investigated at considerable length in a wide variety of chemical processes. Iron(0) carbonyl species are acutely toxic and flammable and therefore present serious handling issues that limit their utility in non-specialist chemical environments. Thousands of tonnes of iron(0) carbonyl compounds are synthesised each year in a handful of specialised production plants, however the vast majority of the material is produced only as an intermediate in the synthesis of high purity iron metal or iron oxides.<sup>124</sup> Carbon monoxide is well known to form strong bonds to metal centres due to the formation of strong  $\sigma$ -bonds with significant  $\pi$ -back-bonding.  $\text{Fe}^0_n(\text{CO})_m$  species therefore tend to be thermodynamically stable and require either chemical, or photo- or thermal irradiation activation processes.<sup>125</sup> When activated in such a manner, an ensemble of coordinatively unsaturated iron(0) carbonyl species can be generated. While the catalytic chemistry of iron(0) carbonyl species has been explored for several decades, due to their toxicity and lack of green chemistry credentials, examples of iron(0) carbonyl catalysed reactions will be only briefly discussed where relevant.

An alternative strategy for accessing active low oxidation-state iron catalysts is to synthesise well-defined iron pre-catalysts, that undergo facile catalyst activation *in situ*. These are typically air- and moisture sensitive, and examples of this strategy include: formally high oxidation-state complexes, bearing ligands that can be triggered into performing a reductive elimination;<sup>126</sup> well-defined formally iron(0) complexes, such as those reported by the group of Chirik; and isolated, well-defined iron(0) nanoparticles.

This strategy is extremely powerful, allowing access to highly active pre-catalysts and tightly controlled reaction conditions. Additionally, since the pre-catalysts undergo facile activation

(typically ligand dissociation or reductive elimination events) this strategy allows the use of simple reaction conditions, without any requirement for chemical or physical means of activation.

Perhaps the most thoroughly investigated class of iron pre-catalyst for hydrogenation and hydrofunctionalisation chemistry is the wide variety of iron(0) complexes ligated by *N*- and *C*-donor ligands reported by the group of Chirik.<sup>12</sup> These complexes are produced by the reduction of the corresponding iron(II) species by strong reductants primarily: sodium amalgam; NaHBET<sub>3</sub>; and sodium naphthalene. The resultant iron(0) complexes are highly active catalysts for various reactions including: hydrogenation, hydrosilylation, hydroboration and [2+2] cycloadditions. These species will be discussed at length in the appropriate sections below.

An alternate strategy to the use of well-defined low oxidation-state complexes is the use of pre-prepared iron nanoparticles. Iron and iron oxide nanoparticles have long been known; much of the investigation into these materials has focused on their magnetic properties, but they have been used in such diverse applications as magnetic fluids,<sup>127</sup> catalysts for carbon-nanotube formation,<sup>128</sup> magnetic resonance imaging contrast agents,<sup>129</sup> environmental remediation,<sup>130</sup> and more recently, catalysts and supports for catalysts for a variety of reactions.<sup>131,132</sup>

Iron nanoparticles have been synthesised by a range of methods.<sup>133</sup> Iron carbonyl compounds, most notably Fe(CO)<sub>5</sub>, can be thermally decomposed in the presence of polymeric or small molecule surfactants to give iron nanoparticles.<sup>134,135</sup> The pathways of Fe(CO)<sub>5</sub> decomposition are very complex, with a range of intermediate iron carbonyl complexes formed. Both surfactants and the intermediate iron complexes can act catalytically for the decomposition resulting in reactions that can change rate and even order during a reaction. Therefore this route to iron nanoparticles is relatively simple to perform, but the shapes and sizes of the resulting particles are rather difficult to predict. Instead of starting with an iron(0) species, iron salts or oxides can be chemically reduced to iron(0) nanoparticles using a range of common reducing agents including, hydrazine, borohydride reagents,<sup>136–138</sup> Grignard reagents,<sup>139</sup> and even tea extract.<sup>140</sup> While there have been several reports of borohydride reagents being used to synthesise iron nanoparticles, other reports have found a range of amorphous iron species containing varying amounts of boron.<sup>138,141</sup> The reduction of iron oxides to nanoparticles does not appear to be regularly used outside certain industrial applications due to the length and complexity of the synthetic pathway. Certain iron organometallics such as {Fe[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>2</sub>} can be decomposed under hydrogenative conditions to nanoparticles.<sup>142</sup> Additionally, routes to Fe<sup>0</sup> nanoparticles by vapour deposition,<sup>143</sup> laser irradiation,<sup>144,145</sup> and milling,<sup>146</sup> have all been reported.

It is illustrative to compare the extremely air- and moisture sensitive Fe<sup>0</sup> pre-catalysts reported by a number of groups with low oxidation-state precious metal catalytic precursors which are commonly commercially available, such as Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>4</sub> or Wilkinson's catalyst [Rh<sup>I</sup>(PPh<sub>3</sub>)<sub>4</sub>Cl]. While these species may be susceptible to oxidation, they can commonly be stored and handled in labs without access to strict air- and moisture free techniques. In contrast, Fe<sup>0</sup> species are highly susceptible to oxidation therefore degrade rapidly and violently enough to be highly pyrophoric.

A third strategy to access low oxidation-state catalytic iron species is to use iron(II/III) pre-catalysts which can undergo activation *in situ* by the addition of a reductant. This strategy allows the use of air- and moisture stable pre-catalysts, and so potentially allows access to iron chemistry for chemists without access to strictly air- and moisture sensitive techniques. To date the vast majority of examples of *in situ* activation of iron complexes have used organometallic reagents with a (conjugate acid) pK<sub>a</sub> of above 36, such as Grignard reagents, NaHBet<sub>3</sub> and LiAlH<sub>4</sub>. The issue of heterotopicity should be considered when this strategy is used, especially when effective chelating ligands are not used.

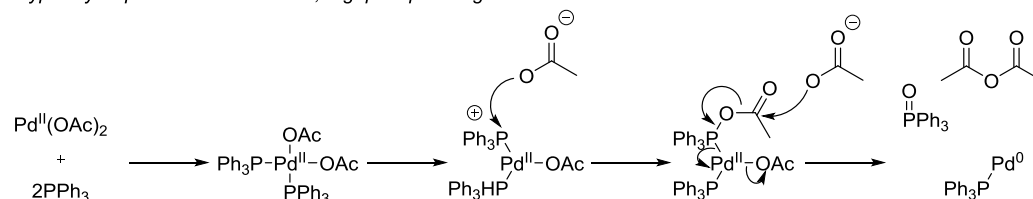
Once again, it is illustrative to compare these iron systems to precious metal pre-catalysts. Pd<sup>II</sup> salts are robust towards air- and moisture, and the standard electrode potential (E°) for Pd<sup>II</sup>/Pd<sup>0</sup> is +0.92 V. This is a thermodynamically favourable reaction, meaning that Pd<sup>0</sup> species can be readily generated from stable Pd<sup>II</sup> salts.<sup>147</sup> Typically Pd<sup>II</sup> salts can be reduced *in situ* by mild processes such as the oxidation of phosphine ligands (Scheme 1.07 a) or amines.<sup>148,149</sup>

In contrast, for Fe<sup>II</sup>/Fe<sup>0</sup>, E° = -0.44 V a thermodynamically unfavourable process, and therefore requires considerable energy input.<sup>147</sup> The *in situ* generation of low oxidation-state iron catalysts therefore requires the use of a strong, typically organometallic, reductant. A representative example, is the reduction of iron(II/III) precursors by Grignard reagents (Scheme 1.07 b), which is proposed to proceed by the following mechanism.<sup>150,151</sup> Alkylation of the iron pre-catalyst **1** results in a bis-alkylated species **2**. This intermediate can undergo a reductive elimination event, performing a 2-electron reduction of the metal centre to give low oxidation-state iron species **3** and generating an equivalent of the oxidatively-dimerised Grignard reagent **4**. Alternatively, if the Grignard reagent bears β-hydrogens, bis-alkylated metal complex **2** can undergo a β-hydride elimination reaction and generate **5**, which can then undergo the reductive elimination step to produce **2**. This second pathway generates an equivalent of alkene **6** and an equivalent of the alkane **7**.<sup>152,153</sup> It should be noted that metal species in solution can also undergo 1-electron reduction processes, and comproportionation or disproportionation reactions, meaning that the oxidation state of species in solution can be difficult to predict.<sup>154–156</sup>

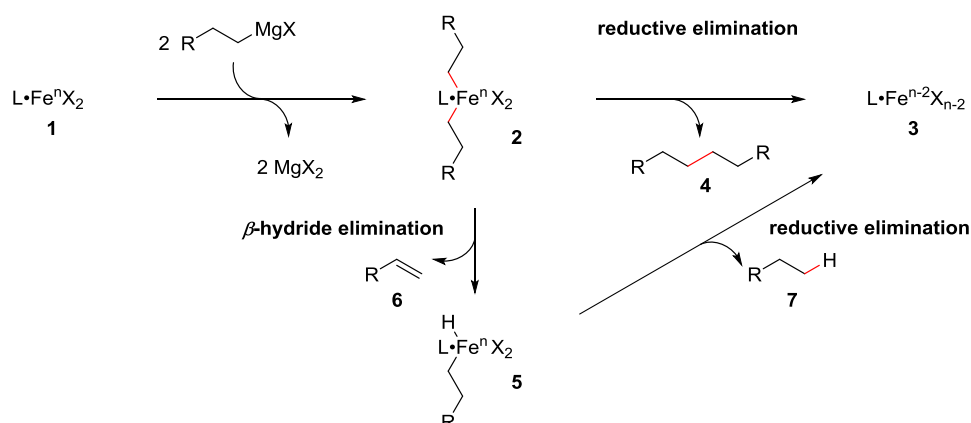


To the best of the author's knowledge, only one example exists of an iron-catalysed hydrosilylation reaction with *in situ* catalyst activation by a less basic reagent.<sup>157</sup>

- a)  $\text{Pd}^{\text{II}} + 2\text{e}^- \longrightarrow \text{Pd}^0 \quad E^\circ = +0.84 \text{ V} \quad \Delta G^\circ = -160.2 \text{ kJ mol}^{-1}$   
Typically requires mild reductants, e.g. phosphine ligand oxidation:



- b)  $\text{Fe}^{\text{II}} + 2\text{e}^- \longrightarrow \text{Fe}^0 \quad E^\circ = -0.41 \text{ V} \quad \Delta G^\circ = +78.9 \text{ kJ mol}^{-1}$   
Typically requires strong reductant, e.g. organometallic reagent:



**Scheme 1.07** a) The standard electrode potential ( $E^\circ$ ) and Gibbs free energy ( $\Delta G^\circ$ ) of the reductions of  $\text{Pd}^{\text{II}}$  to  $\text{Pd}^0$  and an example of a  $\text{Pd}^{\text{II}}$  to  $\text{Pd}^0$  reduction.<sup>147–149</sup> b) The standard electrode potential ( $E^\circ$ ) and Gibbs free energy ( $\Delta G^\circ$ ) of  $\text{Fe}^{\text{II}}$  to  $\text{Fe}^0$  along and an example of this reduction by an alkyl-Grignard reagent.<sup>150,151</sup>

### 1.3 GENERAL AIMS

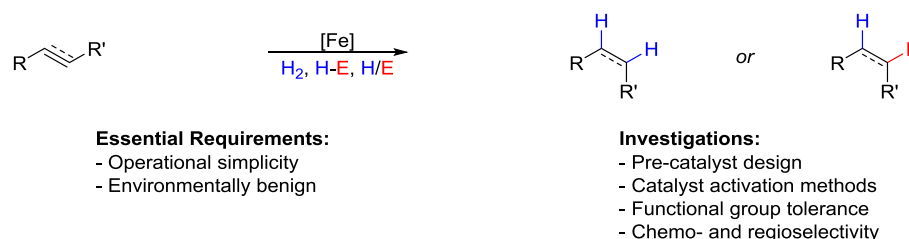
In summary, iron catalysis has been developed greatly in recent years after having been largely side-lined by the chemical community in favour of precious-metal catalysis. Interest in environmentally benign chemistry has reinvigorated the field in recent years, and led to the development of reactions that were typically extremely difficult to perform under ‘traditional’ conditions.

The general aims of the research presented in this work were to expand the existing field of iron catalysis and produce novel reactions for the hydrogenation and hydrofunctionalisation of C-C multiple bonds, constructing new bonds in a controlled and selective manner. Specifically, these reactions were to be operationally simple and reliable, such that they are suitable for use by chemists who are non-experts in iron-catalysis.

While the use of iron offers great advantages in terms of sustainability, cost, toxicity and novel chemistry, it also presents considerable challenges to the investigator. Therefore if the use of iron in catalysis is to become as ubiquitous as the use of precious metals currently is, then the many existing issues with this chemistry must be addressed. The secondary aims of the research presented herein were therefore to develop techniques for performing iron chemistry to bypass these issues.

Firstly, many iron species, particularly those in low oxidation-states are highly air- and moisture sensitive, and their use requires specialist air- and moisture sensitive equipment and techniques. These are not available to most organic chemistry labs in academia and are almost non-existent in an industrial setting. Therefore the development of iron-catalysed reactions robust to air- and moisture sensitive is an important secondary aim of this project.

Secondly, the high redox barriers between oxidation states of iron has to-date required the use of harsh activation methods. The development of novel activation methods for iron pre-catalysts is therefore paramount. Investigations into ligand-assisted modes of catalyst activation are made in Chapter 4.



**Scheme 1.08** General aims of the projects described in this thesis.

These general aims led to the three research projects which are described herein. Firstly, an alkene formal hydrogenation protocol was developed, using sodium borohydride as a stoichiometric reductant, described in Chapter 2. These conditions were then further developed to produce a formal hydrogenation of nitro groups, described in Chapter 3. Finally a group of novel, structurally related alkoxy-tethered *N*-heterocyclic carbene ligated iron(II) complexes were synthesised, and applied to the hydroboration of styrene derivatives, described in Chapter 4.



# CHAPTER 2. OPERATIONALLY SIMPLE, FORMAL HYDROGENATION OF ALKENES USING $\text{Fe}(\text{OTf})_3$ AND $\text{NaBH}_4$

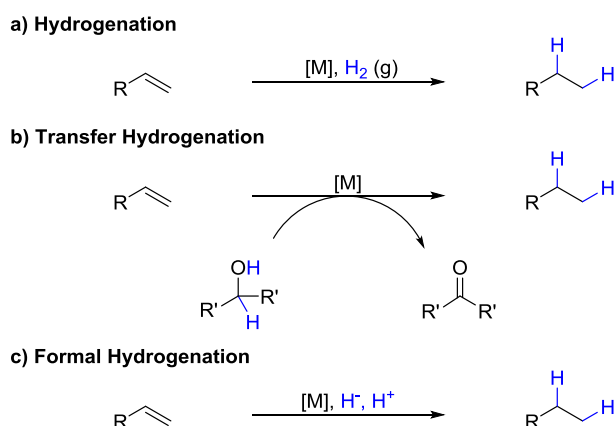
## 2.1 PREAMBLE

Chapter 2 consists of two major sections, the first of which is a background section comprising of: firstly a brief introduction to alkene hydrogenation chemistries; secondly a comprehensive review of recent developments in iron-catalysed alkene hydrogenation reactions; thirdly a summary of the state-of-the-art in iron-catalysed formal hydrogenations of alkenes and the how this project aims to add to the sum of knowledge on the subject. The second section consists of the author's research into developing a novel iron-catalysed formal hydrogenation of alkenes comprising of: work to find the initial leads; optimisation of reaction conditions; the substrate scope of the reaction and cursory mechanistic investigations.

## 2.2 INTRODUCTION

### 2.2.1 ALKENE AND ALKYNE REDUCTION: GENERAL BACKGROUND

The hydrogenation of C-C multiple bonds is a common and important synthetic technique both on an industrial scale and in laboratories.<sup>11,158</sup> Hydrogenation reactions are commonly performed on every feasible scale in the petrochemical, food and fine-chemical industries.



**Scheme 2.01** General schemes for a) hydrogenation, b) transfer hydrogenation and c) formal hydrogenations.

The hydrogenation of a C-C multiple bond is a 2-electron, 2H process, that typically occurs only in the presence of a suitable catalyst. For the purposes of this document, hydrogenation reactions can be roughly categorised according to the terminal reductant used in a system:

hydrogenation reactions use hydrogen gas as a source of 2 electrons and  $2\text{H}^+$  (Scheme 2.01 a); transfer hydrogenations remove an  $\text{H}^-$  and an  $\text{H}^+$  from a ( $\text{sp}^3$ )-system, generating a ( $\text{sp}^2$ )-equivalent (Scheme 2.01 b); and formal hydrogenations require a stoichiometric source of  $\text{H}^-$  and  $\text{H}^+$  (Scheme 2.01 c).

While using hydrogen gas as a terminal reductant offers the possibility of excellent atom economy it is often used in massive excess, somewhat diminishing its 'green' credentials. Additionally many examples of hydrogenation are performed under conditions of elevated temperatures and pressures. Performing reactions at raised temperatures and pressures require: energy input; specialist equipment; and raises safety concerns. This is of enough concern that a great deal of effort and money has been expended on systems that generate small quantities of  $\text{H}_2$  *in situ*.<sup>159</sup> Therefore choosing alternate terminal reductants offers much potential; especially on a small (i.e. laboratory) scale. A formal hydrogenation reaction typically allows the exploitation of reductants in reactions that they would not perform uncatalysed.

The vast majority of C-C multiple bond hydrogenation catalysts are finely divided platinum group metals, in particular the extremely prevalent palladium-on-carbon (Pd/C) and platinum metal and its oxides.<sup>97</sup> Perhaps the most significant first-row transition metal catalysts are highly-activated Raney-,<sup>160,161</sup> and Urushibara- type nickel species.<sup>162,163</sup> These reactions benefit from being well established and thoroughly investigated, therefore reaction conditions and factors affecting the reactions are well understood.

The earliest examples of iron-catalysts for C-C multiple bond hydrogenation reactions were highly-activated heterogeneous species inspired by highly activated Raney-type metals. Thompson and Wyatt produced a solid catalyst for the selective hydrogenation of alkynes to alkenes by the treatment of an iron/aluminium alloy with NaOH. Under 70 atm of  $\text{H}_2$  and 100 °C acetylene derivatives were reduced exclusively to ethylene derivatives.<sup>164,165</sup> Even at this early stage iron catalysts were proposed as alternatives to palladium and nickel, not just due to its abundance and non-toxicity but also due to the possibility of alternative selectivity. Iron- and iron-oxide particles have also been widely used as magnetically-recoverable supports for active precious-metal alkene hydrogenation catalysts.<sup>166–170</sup>

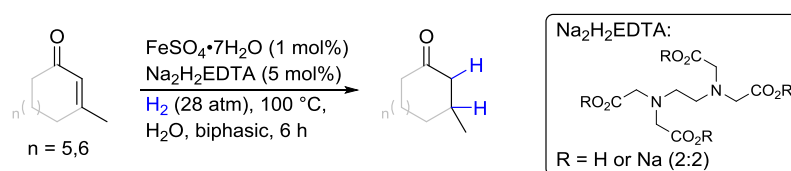
Interestingly, biological systems that utilise hydrogen (hydrogenase enzymes) typically feature iron-sulfur clusters or iron co-factors at the active site.<sup>171</sup> Iron-sulfur clusters have also been synthesised under laboratory conditions,<sup>172,173</sup> and reported for alkene hydrogenation when activated by organometallic reagents.<sup>174,175</sup>

## 2.2.2 RECENT DEVELOPMENTS IN IRON-CATALYSED ALKENE AND ALKYNE REDUCTIONS

There are several recent and comprehensive reviews of the topic of iron-catalysed C-C multiple bond reductions.<sup>66–68</sup> In recent years there has been considerable progress in the field which will be discussed here, along with pertinent older examples.

Alkene and alkyne reductions using iron(0) carbonyl complexes have been known since the 1960s.<sup>176–178</sup> A wide range of  $\text{Fe}_n(\text{CO})_m\text{L}_o$  precursors can be used,<sup>179,180</sup> and mechanistic investigations suggest that the iron(0) carbonyl precursors are decomposed to active  $\text{Fe}(\text{CO})_m\text{L}_o$  species with vacant coordination sites.<sup>181,182</sup> Typically, reactions require heating or continuous irradiation in order to maintain the coordinatively unsaturated active species further diminishing their green chemistry credentials.<sup>183,184</sup> Iron(0) carbonyl species have also been shown to be active hydrogenation catalysts in mixed-metal systems.<sup>185</sup> Due to the difficulty of handling these catalysts and their unique chemistry, these systems will not be further discussed in this work.

Limited examples of thermally-activated iron-catalysed alkene hydrogenations, using simple iron salts, also exist. Notably, Bhanage and co-workers reported the hydrogenation of  $\alpha,\beta$ -unsaturated aldehydes, ketones, esters and carboxylic acids (12 examples, 20–95% yields) under relatively high temperatures and pressures of  $\text{H}_2$  in a biphasic system (Scheme 2.02).<sup>186</sup> Using  $\text{Fe}^{\text{II}}\text{SO}_4 \cdot 7\text{H}_2\text{O}$  and ethylenediaminetetraacetate (EDTA) disodium salt an alkene hydrogenation catalyst is formed, which is retained in the aqueous layer. Similar systems have been previously reported for hydrogenation of *in situ* formed amides.<sup>187</sup> No mechanistic investigations are reported.



**Scheme 2.02** Bhanage and co-workers' hydrogenation of  $\alpha,\beta$ -unsaturated carbonyl systems using simple iron(II) salts and EDTA under thermal conditions.<sup>186</sup>

The examples of iron-catalysed alkene and alkyne hydrogenation shown below are loosely grouped according to both the catalyst activation and alkene reduction strategy.

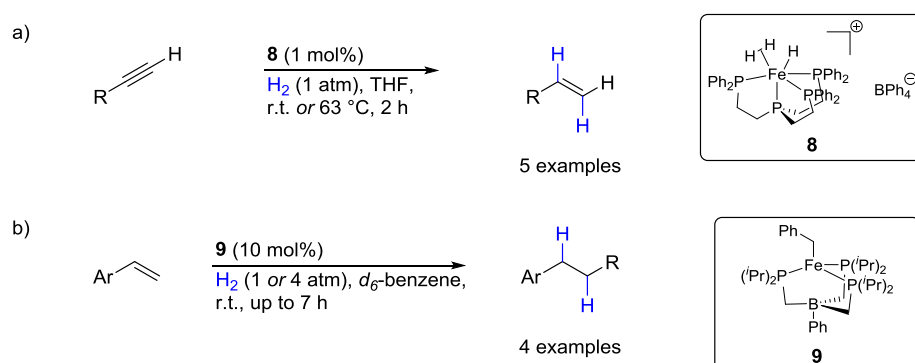
### 2.2.2.1 Pre-Catalysts Bearing Activating Groups for Alkene and Alkyne Hydrogenation

One strategy for the activation of iron-catalysts has been the incorporation of activating groups into the pre-catalyst complex. These complexes are designed such that the pre-catalyst undergoes a facile activation in solution. This is seen clearly in the reports of iron(II) pre-

catalysts supported by multidentate phosphine ligands. In all cases, these complexes supported by multidentate phosphine ligands have been pre-coordinated with an hydridic species capable of activating the catalyst.

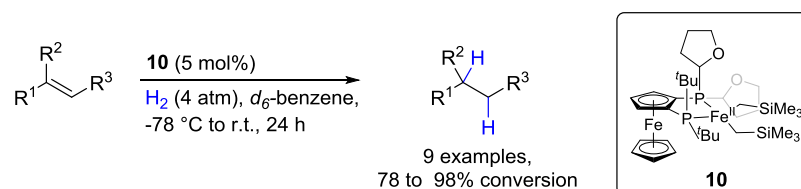
One of earliest developments in ‘modern’ iron-catalysed hydrogenations were the reports by Bianchini and co-workers of the air-stable iron(II) hydride complex **8**, supported by the tetradentate  $P(CH_2CH_2PPh_2)_3$  ligand.<sup>188</sup> This complex was synthesised by reaction of the corresponding Fe-Cl species with  $NaBH_4$ . **8** was reported to be active for the hydrogenation of alkynes under mild conditions (Scheme 2.02 a),<sup>189</sup> and catalytic investigations appeared to suggest that it remains in the iron(II) oxidation state.<sup>190</sup>

The group of Peters has also reported tridentate phosphine ligand-supported iron-alkyl and iron-hydride complexes, including complex **9**, for the hydrogenation of alkenes (Scheme 2.03 b).<sup>191</sup> These complexes were synthesised from the corresponding iron(II) chloride complexes by alkylation with organometallics. Interestingly, an iron(II/IV) redox cycle is proposed in this system.



**Scheme 2.03** Early work on iron-catalysed C-C multiple bond hydrogenation using multidentate phosphine ligands reported by the groups of a) Bianchini,<sup>188–190</sup> and b) Peters.<sup>191</sup>

More recently, the group of Chirik has attempted to use high-throughput screening of libraries of bidentate phosphine ligands and iron salts to identify active iron catalysts for alkene hydrogenation. The resultant complexes were activated with  $LiCH_2SiMe_3$ , but only showed limited hydrogenation activity.<sup>192</sup> Isolated iron(II)phosphine complexes with  $-CH_2SiMe_3$  counterions proved to be more active, and enantioenriched complex **10** was demonstrated to reduce primary, secondary and tertiary alkenes (9 examples, up to 98% conversion, Scheme 2.04). A complete lack of stereo-induction, NMR-silent reaction mixtures and observation of a black precipitate led to investigation into the homogeneity of the reaction mixture. This revealed that the complex decomposed to an amorphous iron(0) colloid. Discrete nanoparticles could not be observed using TEM spectroscopy.

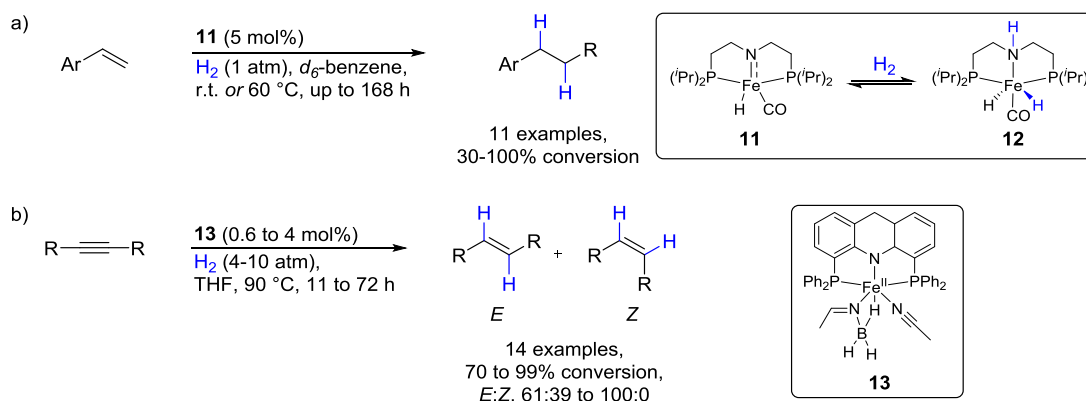


**Scheme 2.04** Iron(II) phosphine complex **10** for alkene hydrogenation as reported by Chirik.<sup>192</sup>

Iron complexes supported by PNP pincer ligands have been investigated at some length for C–O and C–N multiple bond hydrogenations,<sup>193–196</sup> however more recently have been reported by multiple groups to be active C–C multiple bond catalysts. These complexes appear to act by means of metal-ligand cooperativity, splitting of H<sub>2</sub> into an iron-bound H<sup>–</sup> and an H<sup>+</sup> coordinated to the ligand.<sup>197</sup> The polarised nature of these catalysts appears to limit the substrate scope for C–C multiple bond hydrogenation to styrene derivatives,  $\alpha,\beta$ -unsaturated carbonyl derivatives and alkynes.

Jones and co-workers have reported the hydrogenation of styrene derivatives by an PNPFe<sup>II</sup>(CO)H complex **11** (11 examples, 30–100% conversion, Scheme 2.05 a).<sup>198</sup> The PNP donor ligands have been reported to be conformationally flexible allowing changes in complex geometry,<sup>199</sup> and have been previously reported for the reversible hydrogenation of C–O and C–N multiple bonds. Mechanistic investigation and DFT calculations have been used to propose that the reaction proceeds *via* iron-hydride species **12** which can act in a sequential stepwise manner to hydrogenate polarised C=C bonds.

An alternative PNP ligand system has been reported by the group of Milstein, in which the novel iron(II) complex **13**, is active for the (*E*)-selective hydrogenation of alkynes (14 examples, 70–90% conversion, Scheme 2.05 b).<sup>200</sup> The role of the amidoborane ligand remains unclear.



**Scheme 2.05** The use of iron(II) complexes bearing PNP-donor ligands as hydrogenation catalyst, a) alkene hydrogenation reported Jones and co-workers using complex **11**,<sup>198</sup> b) alkyne semi-hydrogenation reported Milstein and co-workers using complex **13**.<sup>200</sup>

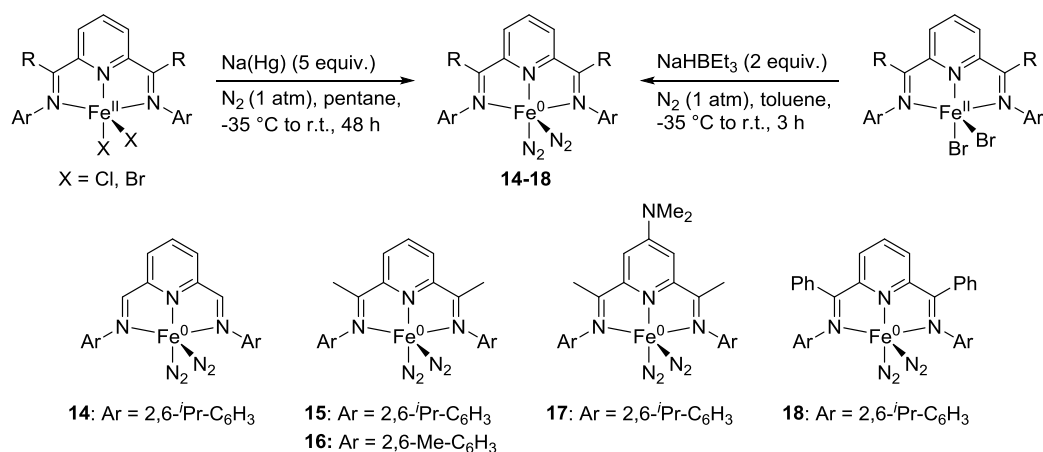


### 2.2.2.2 Low Oxidation-State Iron Pre-Catalysts for Alkene and Alkyne Hydrogenation

An alternative strategy for catalyst activation in iron-catalysed alkene hydrogenation is to use pre-catalysts that have been pre-activated with a strong reductant, then isolated and characterised as low oxidation-state species. The *in situ* activation of this class of pre-catalysts typically consists simply of ligand dissociation steps.

The group of Chirik has been engaged on a research project for over 10 years developing iron catalysts active for a range of chemical transformations of alkenes including: [2+2] cyclisation, hydrosilylation, hydroboration (see Section 4.2.3.4), and hydrogenation.<sup>12</sup> The main theme of this research has been developing complexes with low oxidation-state iron centres bearing redox non-innocent, chelating N and C donor ligands.

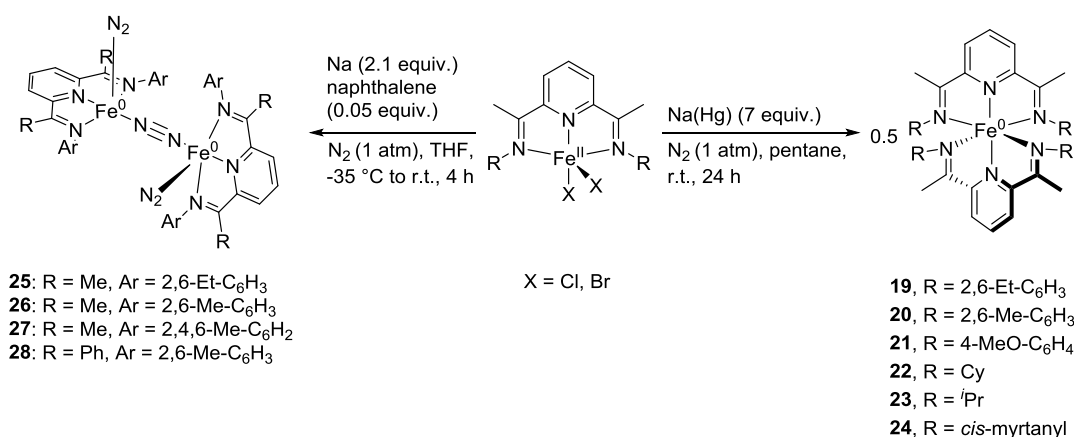
Inspired by the polymerisation catalysts of Gibson<sup>201,202</sup> and Brookhart,<sup>203–205</sup> the group of Chirik took various iron(II) bis(imino)pyridine (BIP) complexes and reduced them under strictly air and moisture free condition to give the corresponding iron(0) bis(imino)pyridine complexes (**14** to **18**, Scheme 2.06).<sup>206–209</sup> These complexes are typically synthesised under an N<sub>2</sub> atmosphere, resulting in 18-electron, 5-coordinate, complexes saturated with weakly coordinating N<sub>2</sub> ligands of the general type BIPFe<sup>0</sup>(N<sub>2</sub>)<sub>2</sub>, and were intended to be mimics of iron(0) carbonyl fragments. Alternative neutral ligands, such as butadiene or CO, can also be introduced either by synthesising the complexes under an alternative atmosphere, or by displacement of N<sub>2</sub> in order to modify the stability of the complexes and further diversify the family of complexes.<sup>208</sup> Upon solvation, it appears as though one of the N<sub>2</sub> ligands rapidly dissociates to give 4-coordinate complexes of the general type BIPFe<sup>0</sup>(N<sub>2</sub>).<sup>210</sup>



**Scheme 2.06** A sample of the BIPFe<sup>0</sup>(N<sub>2</sub>)<sub>2</sub> complexes (**14-18**) produced by the group of Chirik.<sup>206–209</sup>

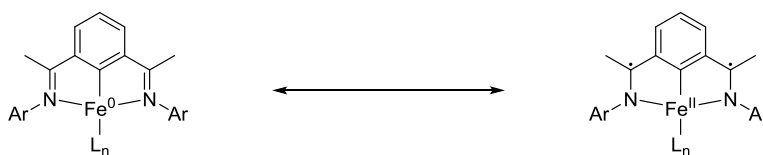
The modularity of bis(imino)pyridine ligands allowed the synthesis of a wide range of sterically- and electronically differentiated complexes.<sup>211</sup> This included variation of the steric bulk of the groups on the imine nitrogen, and carbon atoms, the addition of electron-donating and – withdrawing groups on the 4 position of the pyridine group. In practice it was found that complexes bearing ligands with little steric bulk on the imine-nitrogen formed the coordinatively saturated complexes **19-24** (Scheme 2.07), these were completely inert and not catalytically active.

For certain less-bulky ligands, the formation of coordinatively saturated complexes could be inhibited by performing the reduction reaction with sodium/naphthalene in THF. This produced nitrogen-bridged dimers of the iron(0)bis(imino)pyridine complexes (**25-28**, Scheme 2.07), which act as effective pre-catalysts for a variety of reactions.<sup>212</sup>



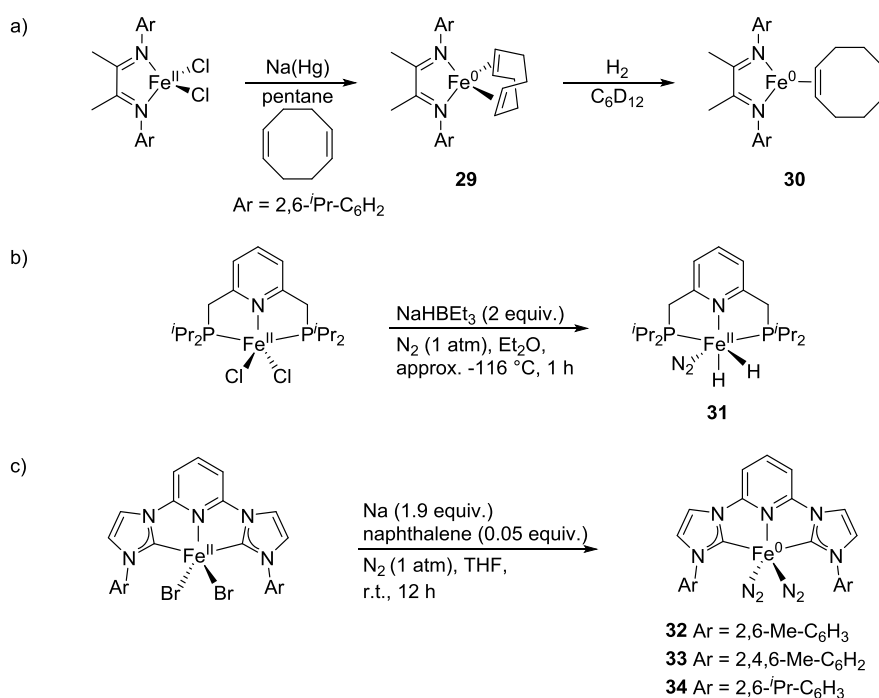
**Scheme 2.07** Sterically unencumbered BIPFe<sup>0</sup>L<sub>n</sub> complexes **25-28** present a greater synthetic challenge due to the potential formation of coordinatively saturated species **19-24**.<sup>212</sup>

The BIP ligands used in this work are redox non-innocent: capable of both receiving and accepting electron density. Thanks to this property, they are able to modulate the reactivity of the metal centre to which they are ligated.<sup>214,215,217</sup> Chirik has credited this electronic non-innocence with shifting the reactivity of these complexes away from the 1-electron chemistry, with which iron is traditionally associated, towards 2-electron type chemistry.<sup>216</sup> The group of Chirik has used NMR, IR, and Mössbauer spectroscopy, X-ray crystallography and computational studies to probe the electronic structure of the BIPFe<sup>0</sup>L<sub>n</sub> complexes with various neutral ligands. These formally iron(0) complexes appear to exist as hybrids of iron(0) complexes with neutral ligands and iron(II) complexes with dianionic ligands (Scheme 2.08).<sup>218</sup>



**Scheme 2.08**  $\text{BIPFe}^0\text{L}_n$  complexes exist as hybrids of an  $\text{Fe}^0$  complex in a neutral ligand and an  $\text{Fe}^{\text{II}}$  complex in a di-radical ligand.<sup>218</sup>

Chirik and co-workers have attempted to produce activated iron complexes supported by a number of other ligand families including:  $\alpha$ -diimine (DI) ligands to give  $\text{DIFe}^0\text{L}$  complexes **29** and **30** (Scheme 2.09 a);<sup>219</sup> and bis(diisopropylphosphino)pyridine (PDI) ligands to give, formally iron(II) dihydride, complex  $\text{PDIFe}^{\text{II}}(\text{N}_2)\text{H}_2$  **31** (Scheme 2.09 b).<sup>220</sup> Additionally, using the chelating CNC donor  $N$ -heterocyclic carbene (NHC) ligands first reported by Danopoulos,<sup>221</sup> the group of Chirik has reported complexes  $\text{CNCFe}^0(\text{N}_2)$  **32-34** (Scheme 2.09 c).<sup>222</sup> As with his previous reports, these complexes were produced by the controlled reduction of the corresponding  $\text{Fe}^{\text{II}}$  precursor.

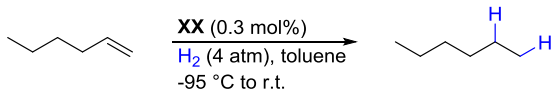
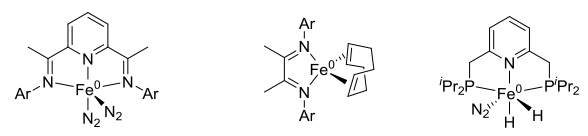


**Scheme 2.09** Chirik and co-workers' syntheses of a)  $\text{DIFe}^0\text{L}$  complexes **29** and **30**,<sup>219</sup> b)  $\text{PNPF}^{\text{II}}(\text{N}_2)\text{H}_2$  **31**,<sup>220</sup> and c)  $\text{CNCFe}^0(\text{N}_2)_2$  complexes **32-34**.<sup>222</sup>

Chirik and co-workers have been systematic in their assessment of the catalytic activity of their reported complexes, allowing useful comparisons of their activity to be made. The  $\text{BIPFe}^0(\text{N}_2)_2$  complexes (**15**) were demonstrated to be highly effective pre-catalysts for the hydrogenation of simple alkenes: 1-hexene could be hydrogenated in 12 minutes at room temperature, under 4 atm of  $\text{H}_2$ , and at 0.3 mol% catalyst loading (Table 2.2-1). The  $\text{DIFe}^0\text{L}$  complex **29** and

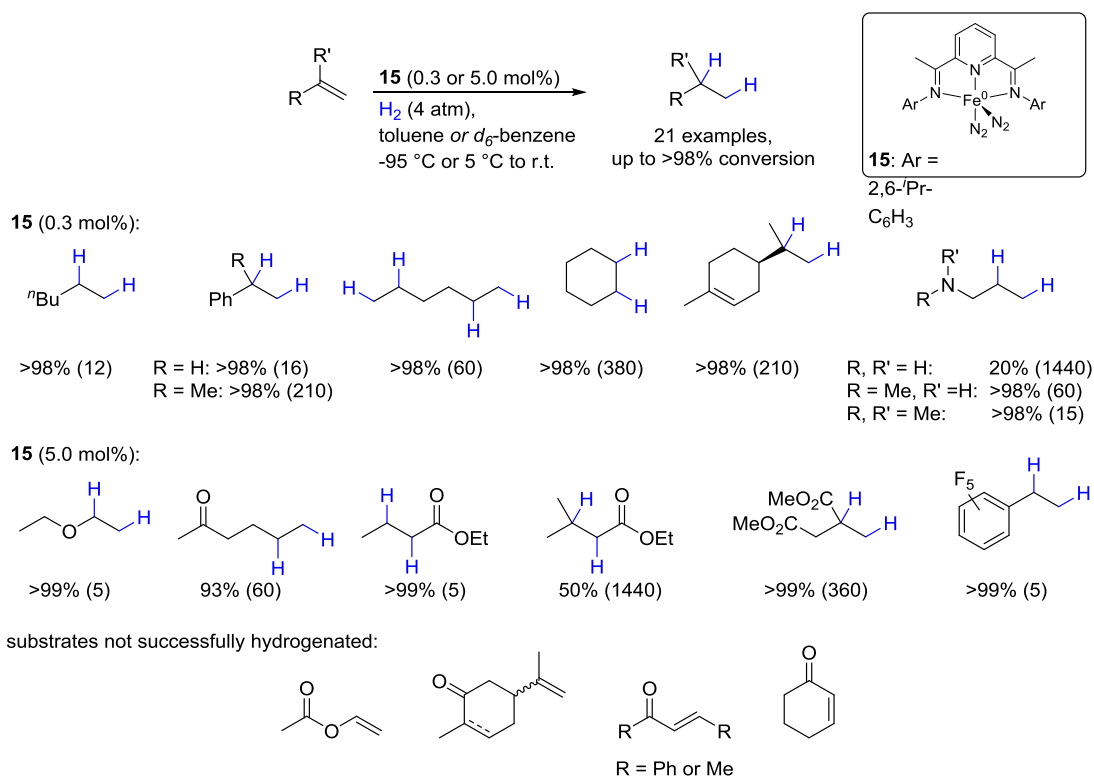
PDIFe<sup>II</sup>(N<sub>2</sub>)H<sub>2</sub> **31** were considerably less active catalysts for the hydrogenation of 1-hexene than the BIPFe<sup>0</sup>L<sub>2</sub> family of complexes taking 240 minutes and 180 minutes to reach completion respectively. Further investigation of the catalytic hydrogenation activity of **29** and **31** was not performed due to their poor performance with simple substrates.

**Table 2.2-1 Comparison of the catalytic activities of complexes 15, 29 and 31 for the hydrogenation of 1-hexene.**<sup>219,220,223</sup>

			
			
	<b>15</b> : Ar = 2,6- <i>i</i> -Pr-C <sub>6</sub> H <sub>3</sub>	<b>29</b> : Ar = 2,6- <i>i</i> -Pr-C <sub>6</sub> H <sub>3</sub>	<b>31</b>
Conversion (time):	>95% (12)	>95% (240)	>95 (180)

<sup>a</sup>Conversions, as calculated by GCMS or <sup>1</sup>H NMR spectroscopy reported, values in parentheses are times to complete conversion (min).

Initial investigations into the substrate scope of the **15** catalysed alkene hydrogenation, showed the complex to be catalytically competent for the hydrogenation of: alkyl- and aryl- substituted terminal; 1,1-disubstituted; and 1,2-disubstituted alkenes at low catalyst loadings (**15** [0.3 mol%], 9 examples, up to 98% conversion, Scheme 2.10).<sup>223</sup> Further substrate scope investigations revealed **15** to be an effective pre-catalyst for alkenes bearing both polar functional groups such as ethers and secondary amines; and reducible functional groups such as esters and some ketone substituents, albeit requiring higher catalyst loading (**15** [5.0 mol%], 12 examples, up to 98% conversion, Scheme 2.10).<sup>224</sup> Tri-substituted alkenes could only be reduced if they were polarised by conjugation with an electron-withdrawing group.  $\alpha,\beta$ -Unsaturated ketones resulted in rapid decomposition of the complex, however  $\alpha,\beta$ -unsaturated esters were tolerated by the iron catalysts.

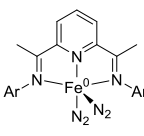
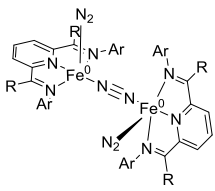
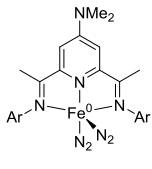
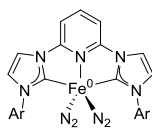
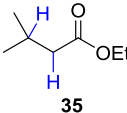



**Scheme 2.10** Substrate scope for the  $i^{\text{Pr}}\text{BIPFe}^0(\text{N}_2)_2$  complex **15** catalysed alkene hydrogenation.<sup>223,224</sup>

Conversions, as calculated by GCMS or  $^1\text{H}$  NMR spectroscopy reported, values in parentheses are times to complete conversion (min).

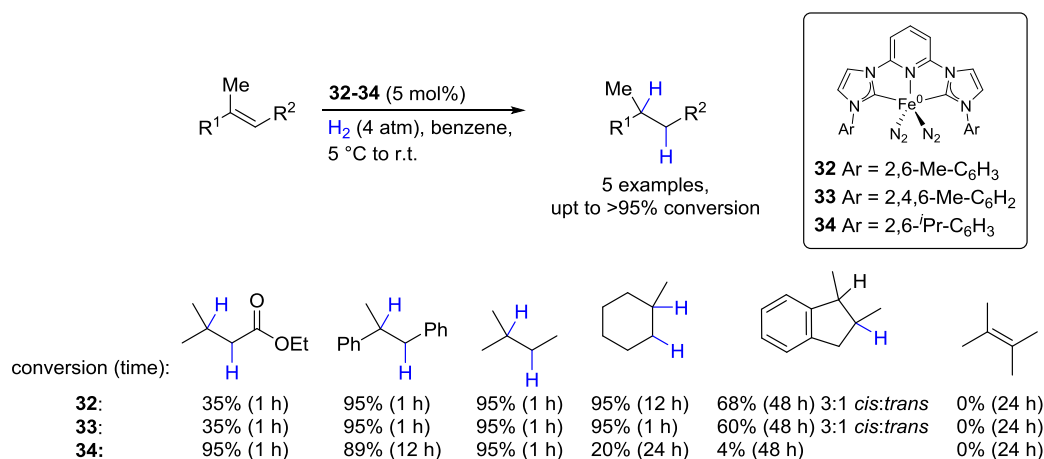
While the diisopropyl-substituted  $i^{\text{Pr}}\text{BIPFe}^0(\text{N}_2)_2$  complex **15** has been demonstrated to be an excellent catalyst for simple alkenes, long reaction times and higher catalyst loadings were required for more heavily substituted and functionalised alkenes. In order to overcome these shortcomings, the large variety of  $\text{Fe}^0$  pre-catalysts produced by the group of Chirik were screened for catalytic activity in the hydrogenation of more challenging substrates: ethyl- 3,3-dimethylacrylate **35** and 1-methylcyclohexene **36** at 0.3 mol% catalyst loading and  $\text{H}_2$  (4 atm) (Table 2.2-2). The less-sterically encumbered complex **26** and the relatively electron-rich complex **17** were both more active than complex **15** for the hydrogenation of ethyl- 3,3-dimethylacrylate **35**. The  $\text{CNCFe}^0(\text{N}_2)_2$  complexes **32** and **34** were the only reported  $\text{Fe}^0$  complexes that was active for the hydrogenation of unactivated tertiary alkene **36**.

**Table 2.2-2 Investigation into catalytic activity of iron(0) complexes for the hydrogenation of challenging substrates: ethyl- 3,3-dimethylacrylate and 1-methylcyclohexene, by the group of Chirik.**<sup>212,222</sup>

	$\text{R}-\text{CH}=\text{CH}_2 \xrightarrow[\text{5 } ^\circ\text{C to r.t.}]{\text{[Fe] (0.3 mol\%), H}_2 \text{ (4 atm), benzene}} \text{R}-\text{CH}_2\text{CH}_3$			
	 <b>15:</b> Ar = 2,6- <i>i</i> -Pr-C <sub>6</sub> H <sub>3</sub>	 <b>26:</b> R = Me, Ar = 2,6-Me-C <sub>6</sub> H <sub>3</sub>	 <b>17:</b> Ar = 2,6- <i>i</i> -Pr-C <sub>6</sub> H <sub>3</sub>	 <b>32:</b> Ar = 2,6-Me-C <sub>6</sub> H <sub>3</sub> <b>34:</b> Ar = 2,6- <i>i</i> -Pr-C <sub>6</sub> H <sub>3</sub>
Conversion (time):				
 <b>35</b>	50% (24 h)	>95% (1.5 h)	>95% (7 h)	<b>32:</b> 35% (1 h) <b>34:</b> >95% (1 h)
 <b>36</b>	0% (24 h)	2% (24 h)	3% (24 h)	<b>32:</b> >95% (12 h) <b>34:</b> 20% (24 h)

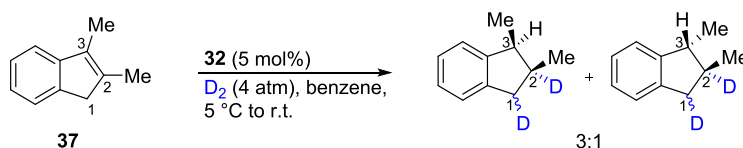
<sup>a</sup>Conversions, as calculated by GCMS or <sup>1</sup>H NMR spectroscopy reported, values in parentheses are times to complete conversion (h).

Given this reactivity, CNCFe<sup>0</sup>(N<sub>2</sub>)<sub>2</sub> complexes **32-34** were assessed for the hydrogenation of a range of tertiary and quaternary alkenes.<sup>222</sup> These complexes were shown to successfully hydrogenate alkyl-, aryl- and ester- substituted tertiary alkenes, in good yield and without cleavage of the ester (5 examples, 68-95% conversion) at 23 °C and H<sub>2</sub>(4 atm). Significantly the **32** or **33** catalysed reduction of 2,3-dimethylindine **37** was also reported; this is the first report of the iron-catalysed reduction of a quaternary alkene (Scheme 2.11).



**Scheme 2.11** Substrate scope for the  $\text{CNCFe}^0(\text{N}_2)_2$  complexes **32-34** catalysed hydrogenation of sterically encumbered alkenes.<sup>222</sup>

While the reduction of 2,3-dimethylindene **37** is no doubt significant,  $\text{CNCFe}^0(\text{N}_2)_2$  complexes **32** and **33** did not prove to be a general catalyst for the hydrogenation of quaternary alkenes. Deuterium labelling experiments showed deuterium incorporation at both the 1- and 2-positions, indicating that the reduction proceeds by isomerisation to the tertiary alkene (Scheme 2.12).



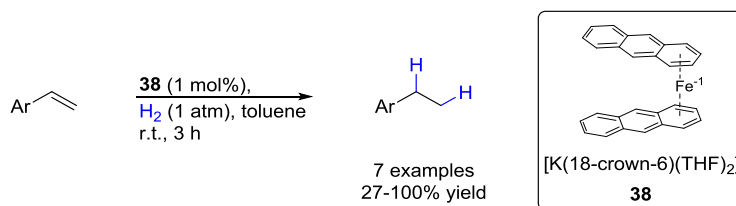
**Scheme 2.12** While  $\text{CNCFe}^0(\text{N}_2)_2$  complex **32**, is active for the hydrogenation of quaternary alkene **37**, deuterium labelling experiments show that this proceeds by isomerisation to the tertiary alkene.<sup>222</sup>

The work of Chirik and co-workers represents the most systematic and detailed investigation into iron-catalysed alkene and alkyne hydrogenation, giving useful and comprehensive investigation into the activity of a wide range of related iron(0) complexes. These complexes represent an important bench-mark of reactivity for iron catalysts achieving: the hydrogenation of primary, secondary and tertiary alkenes; low catalyst loadings (generally 0.3 mol% for unfunctionalised alkenes, up to 5 mol% in the case of more functionalised substrates); mild reaction conditions (generally ambient temperatures and 4 atm  $\text{H}_2$  pressure); and in some cases, good functional group tolerance.

This collection of iron(0) complexes, reported by the Chirik group, are pre-catalysts whose structure is extremely similar to that of the proposed active catalyst. The only activation event required is loss of a labile  $\text{N}_2$  ligand to produce a coordinatively unsaturated complex. However all the examples of formally iron(0) compounds suffer from: being highly air- and moisture-sensitive; requiring lengthy syntheses; and requiring substrates to be purified prior to use. This

lack of operational simplicity for use means that outside of very well controlled laboratory conditions, these catalysts are largely unusable. In addition, the inherent toxicity of the bisiminopyridine class of ligands means that these catalysts are not particularly suitable for widespread adoption in either an academic or industrial settings.

Jacobi von Wangelin and co-workers have developed an interesting and novel approach to accessing low oxidation-state metal centres. Reduction of either  $\text{CoBr}_2$  or  $\text{FeBr}_2$  with potassium/anthracene resulted in bis(anthracene)metallates such as **38**.<sup>225</sup> The resultant complexes were used shown to be active for the reduction of alkenes (Scheme 2.13). Complex **38** was only active for a limited selection of terminal alkenes whereas the corresponding cobalt(-I) complex was much more active.



**Scheme 2.13** Bis(anthracene) $\text{Fe}^{-\text{I}}$  complex **38** reported by the group of Jacobi von Wangelin.<sup>225</sup>

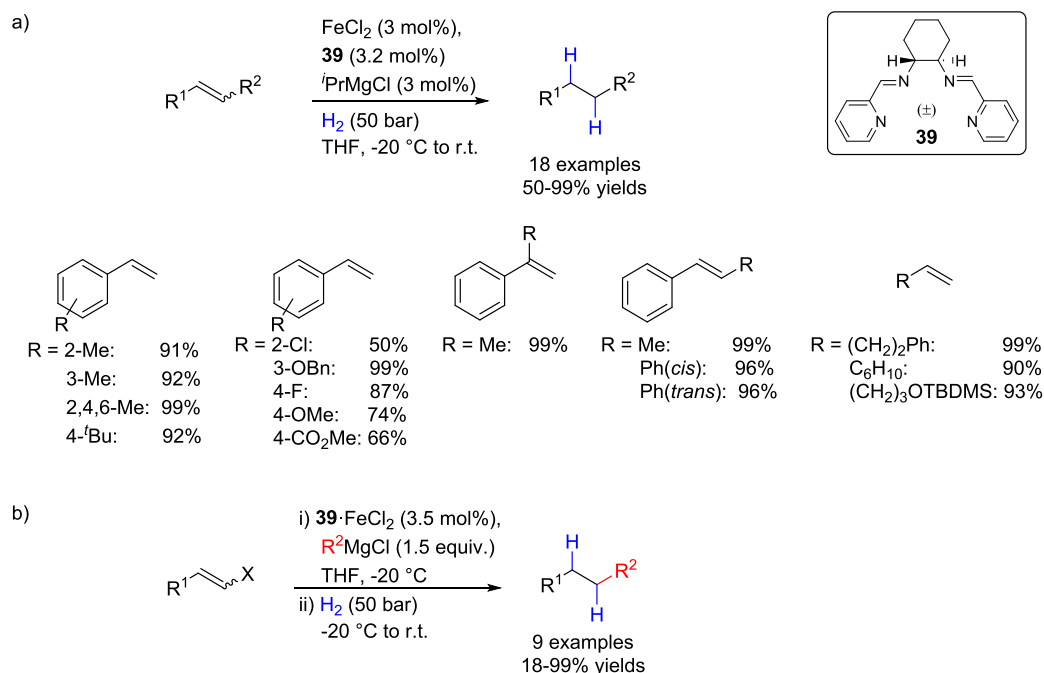
#### 2.2.2.3 *In Situ* Activation of High Oxidation-State Iron Pre-Catalysts for Alkene and Alkyne Hydrogenation

Rather than using highly activated pre-catalysts, a common strategy for iron-catalysed hydrogenation reactions is to activate an air- and moisture stable pre-catalyst *in situ*, typically by use of an organometallic reductant.

The group of Thomas developed a system in which an iron(II) pre-catalyst is activated *in situ* by the addition of a Grignard reagent.<sup>226</sup> A tetradentate *N*-donor ligand (**39**) appears to act to limit aggregation, and the resulting low-valent iron species is active for the hydrogenation of alkenes at r.t. and under  $\text{H}_2$  (50 atm) (Scheme 2.14 a). Styrene derivatives (16 examples, 50-99% yield) including 1,1- and 1,2- disubstituted alkenes were reduced with good yield, as were alkyl- alkenes (3 examples, 90-99% yield). Chloro-, fluoro-, ether and ester functionalised styrenes were all reduced without protodehalogenation or reduction of  $\text{C=O}$  bonds.

In order to exploit the activity of low-valent iron species as catalysts for both cross-coupling reactions and alkene reductions, one-pot reductive cross-coupling reactions were also performed (Scheme 2.14 b). A Grignard reagent was used in stoichiometric amounts to act as both the activating agent for the catalyst and also the coupling partner for a halo- substituted alkene. The resulting 1,2-disubstituted alkene was then reduced under an atmosphere of hydrogen.

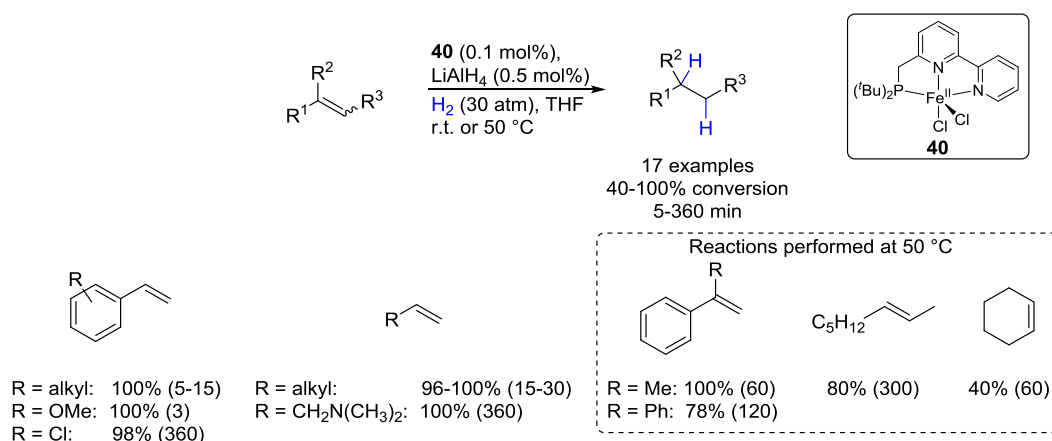




**Scheme 2.14** Thomas and co-workers' *in situ* activation of iron(II)chloride pre-catalysts with Grignard reagents for a) alkene hydrogenation and b) reductive cross-coupling.<sup>226</sup>

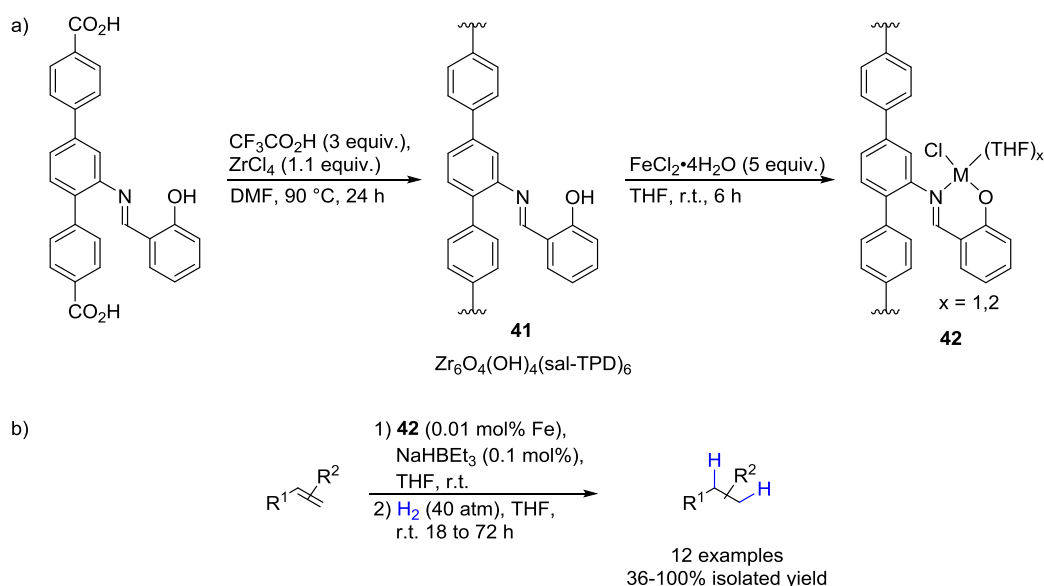
The group of Zhu has reported a thorough investigation into alkene hydrogenation using iron(II) pre-catalysts activated with organometallic reagents.<sup>227</sup> *i*PrBIPFe<sup>II</sup>Cl<sub>2</sub> complex was used as a standard pre-catalyst to screen organometallic activators. NaBEt<sub>3</sub>H, LiAlH<sub>4</sub> and Mg all formed poorly-defined iron species that were highly active for the hydrogenation of alkenes under H<sub>2</sub> (30 atm) at room temperature. In contrast to the results of Thomas and co-workers using the tetradentate ligand **39**,<sup>226</sup> *i*PrMgCl produced only a partially active catalytic species (20% hydrogenation of styrene after 18 h, H<sub>2</sub> [30 atm], r.t.). Proceeding with LiAlH<sub>4</sub> as the activator, iron(II) chloride and a wide range of multidentate *N*- and *P*- donor ligands were screened for hydrogenation activity. In general, ligands with pyridyl- or imino-, N(sp<sup>2</sup>) donor nitrogens (such a bipyridine) showed the highest activity. In contrast, the use of sp<sup>3</sup> hybridised *N*- donor ligands (such as TMEDA) or simple phosphines (such as PPh<sub>3</sub>) produced complexes that were inactive for hydrogenation under these conditions. Multidentate phosphine ligands were capable of supporting active hydrogenation catalysts, but the hydrogenation reactions took significantly longer than with *N*-donors and produced iron particles. This is consistent with reports from Chirik regarding *P*-donor ligands.<sup>192</sup> Complex **40**, bearing a PNN donor ligand, gave complete hydrogenation of styrene at 0.1 mol% catalyst loading in under 5 minutes, so was used to investigate substrate scope. While complex **40** was most active, it should be noted that the isolated ligand is air- and moisture sensitive and requires a laborious synthesis.

The reported catalytic system of  $\text{PNNFe}^{\text{II}}\text{Cl}_2$  **40** and  $\text{LiAlH}_4$  was active for the hydrogenation of styrene derivatives including those with  $\alpha$ -substituents (9 examples, 78-100% conversion, Scheme 2.15). The reaction tolerated chloro- and methoxy- functionalised styrenes, but no other functional groups were reported. Terminal- and 1,1-disubstituted alkyl- alkenes were also successfully hydrogenated (6 examples, 96-100% conversion) including a dimethylamino-functionalised example. 1,2-disubstituted alkenes were considerably less reactive towards these conditions (2 examples, 40-80% conversion). NMR spectroscopy studies suggested the existence of an Fe-H species that undergoes exchange with  $\text{D}_2$ . Interestingly, reactions of styrene with  $\text{D}_2$  gas revealed considerable redistribution of the D-label to the terminal position.



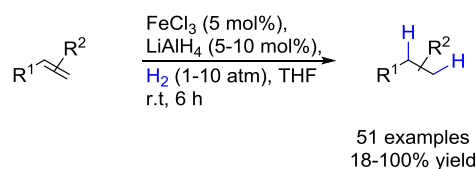
**Scheme 2.15** Hydrogenation of alkenes using  $\text{PNNFe}^{\text{II}}\text{Cl}_2$  complex **40**, activated by  $\text{LiAlH}_4$ , time to complete conversion (min) in parentheses.<sup>227</sup>

Lin and co-workers attempted to synthesise iron(II) complexes with salicylate ligands, and found that  $\text{Fe}_4(\text{sal})_4\text{Cl}_4(\text{THF})_2$  clusters were formed. Attempts to activate these clusters with  $\text{NaBHET}_3$  to produce active alkene hydrogenation catalysts were unsuccessful. This corroborates the other examples in this section where bidentate ligands are insufficient to limit aggregation of the *in situ* formed iron species. The same group have also produced Metal Organic Frameworks (MOFs) incorporating the salicylate motif **41**, which were then functionalised with  $\text{FeCl}_2$  to produce **42**, with an iron loading of 66% (Scheme 2.16 a).<sup>228</sup> MOF **42** was shown to be active for alkene hydrogenation, when activated with  $\text{NaBHET}_3$ , at extremely low loading of iron (12 examples, 36-100% isolated yield, Scheme 2.16 b). The high activity of the solid supported catalysts was proposed to be due to the prevention of aggregation of the active iron centres. The solid MOFs were readily also recoverable, and recyclable.



**Scheme 2.16** Lin and co-workers MOF-supported salicylate  $\text{Fe}^{\text{II}}$  complex **42** is active for alkene hydrogenation when activated with  $\text{NaHBET}_3$ .<sup>228</sup>

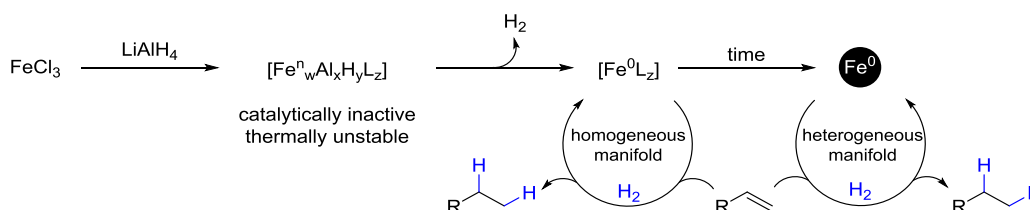
Simple iron(III) salts have been demonstrated to be active hydrogenation catalysts when activated by alkyl-aluminium species to form Ziegler-type catalysts.<sup>229–231</sup> More recently,  $\text{LiAlH}_4$  has been used to activate iron(III) chloride in non-ligated catalytic systems for alkene hydrogenation by the group of Jacobi von Wangelin (Scheme 2.17).<sup>81</sup> An excellent substrate scope was demonstrated for this system including: terminal and  $\alpha/\beta$ -substituted styrene derivatives (28 examples, 18-100% yield); allylbenzene derivatives (8 examples, 79-100% yield); a variety of terminal-, 1,1-disubstituted and 1,2-disubstituted alkyl-alkenes (11 examples, 21-100% yield); and internal alkynes (4 examples, 75-100% yield, (*Z*)-selective semi-hydrogenation or complete hydrogenation depending on reaction time). Across these classes of substrates, the system demonstrates excellent chemoselectivity tolerating: ethers, fluorides, chlorides and bromides (with <12% dehalogenation), esters, amides and pyridyl- groups. Compared to the other examples of iron-catalysed hydrogenation activated with organometallic reagents, this system requires low  $\text{H}_2$  pressures (1 to 10 atm).



**Scheme 2.17** Jacobi von Wangelin and co-workers have demonstrated that an active alkene-hydrogenation system can be produced from  $\text{FeCl}_3$  activated with  $\text{LiAlH}_4$ .<sup>81</sup>

This mechanism of this system was probed with: kinetic poisoning experiments using dibenzo[*a,e*]cycloocta-tetraene (DCT); crystallisation of potential catalytic intermediates; catalyst ageing experiments, deuterium labelling; and the use of radical probes. These investigations

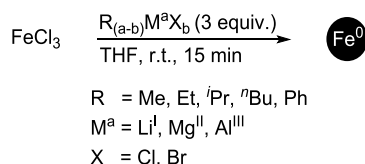
implicate catalyst maturation from discrete, soluble, low oxidation-state to nanoparticulate species over the course of the reaction. This type of catalyst maturation probably occurs to a significant degree in a large number of iron-catalysed reductive transformations, particularly those that do not use chelating ligands. Further investigation into the mechanism demonstrated that the reaction proceeds by a reversible hydro-ferration in a 2-electron manner



**Scheme 2.18** The group of Jacobi von Wangelin have demonstrated the maturation of the catalytic species from initial homogeneous manifold, to heterogeneous manifold.<sup>81</sup>

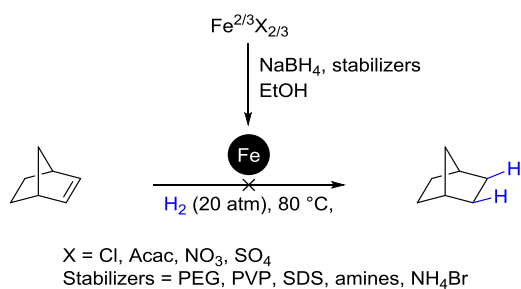
#### 2.2.2.4 Nanoparticulate Iron-Catalysts for Alkene and Alkyne Hydrogenation

In many examples of iron-catalysis, a great deal of optimisation work has been performed in order to prevent the production of iron nanoparticles.<sup>232</sup> However groups researching iron-catalysed cross-coupling reactions have demonstrated that a wide range of pre-catalysts are active if the reaction mixtures were allowed to become colloidal.<sup>139</sup> Additionally, catalyst maturation from discrete species to colloidal systems (*vide supra*) have demonstrated that low oxidation-state iron nanoparticles can be effective hydrogenation catalysts.<sup>81,192</sup>



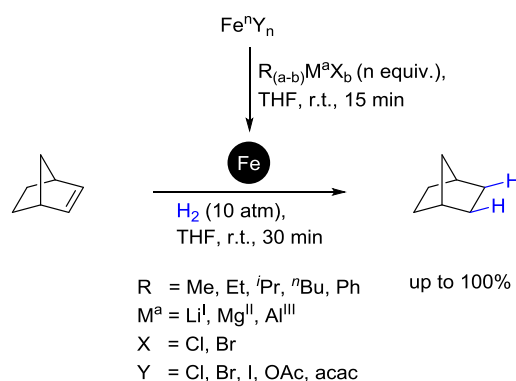
**Scheme 2.19** Iron nanoparticles: generic syntheses.

Given the huge variety of sizes and compositions available under the umbrella title of ‘nanoparticles’, the group of de Vries has used high-throughput techniques to systematically investigate the catalytic activity of a large number of iron nanoparticles synthesised by the reduction of iron salts. The hydrogenation of norbornene was used to assay the catalytic activity of the resulting nanoparticles.<sup>86</sup> Iron nanoparticles synthesised by the reduction of iron salts with  $\text{NaBH}_4$ , in the presence of various stabilisers, all proved to be catalytically inactive for alkene hydrogenation (Scheme 2.20).



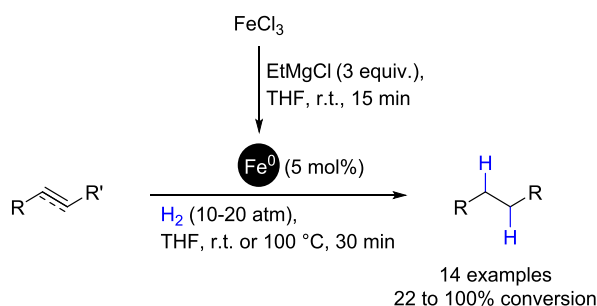
**Scheme 2.20** Nanoparticles produced by reductions of iron(II/III) salts are inactive for the hydrogenation of norbornene.<sup>86</sup>

The group of de Vries then turned to screening of organometallic reductants, in the absence of stabilisers. The iron species resulting from the reduction of  $\text{FeCl}_3$  with 3 equivalents of Li and Mg organometallics were highly active for the hydrogenation of norbornene to norbornane at  $25^\circ\text{C}$  and 10 bar of  $\text{H}_2$  in 30 minutes (Scheme 2.21). The reduction of  $\text{FeCl}_3$  with aluminium organometallics produced considerably less active species. Intriguingly, and in contrast with the results of Bogdanović and Fürstner,<sup>150,233</sup> organometallics unable to undergo  $\beta$ -hydride elimination proved to be capable of reducing  $\text{Fe}^{\text{III}}$  salts to active catalytic species. Iron(II) and iron(III) salts with halide, OAc and acac ligands were all successfully converted into iron species active for norbornene hydrogenation with  $\text{EtMgBr}$ . In all cases, a minimum of 2 or 3 equivalents of the reductant was required to produce an active species from iron(II) or iron(III) salts respectively, implying an average oxidation state of iron(0) in the active catalyst(s). Characterisation of the iron species resulting from the reduction of  $\text{FeCl}_3$  with  $\text{EtMgCl}$  was performed by TEM, SQUID magnetometry and EDX. These techniques revealed iron(0) nanoparticles with an average size of  $2.67 \pm 0.60$  nm that appeared to be stabilised by  $\text{MgCl}_2$ . Given that it was not apparent whether the nanoparticles were the active catalyst or a reservoir for an homogenous species, selective poisoning experiments were performed: these were inconclusive.



**Scheme 2.21** Iron nanoparticles active for the hydrogenation of norbornene can be formed by the activation of a wide range of iron(II/III) salts with Li, Mg and Al organometallics.<sup>86</sup>

The optimised nanoparticle synthesis of FeCl<sub>3</sub> with EtMgCl (3 equiv.) was extremely similar to that reported by Bedford *et al* for the cross-coupling of alkyl halides with aryl Grignard reagents.<sup>139</sup> These optimised conditions were used to investigate the substrate scope of the hydrogenation reaction.<sup>234,235</sup> These nanoparticles were active for the hydrogenation of primary and secondary alkenes and alkynes (14 examples, 22-100% conversion, Scheme 2.22).

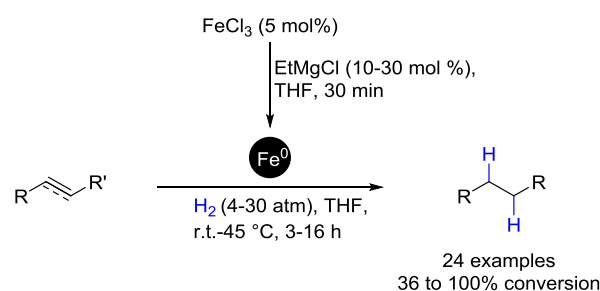


**Scheme 2.22** Conditions reported by the group of de Vries for the *in situ* generation of iron(0) nanoparticles active for alkene and alkyne hydrogenation.<sup>86,234</sup>

The group of Jacobi von Wangelin has also developed a hydrogenation catalyst produced by the reduction of FeCl<sub>3</sub> with EtMgCl.<sup>89</sup> The resulting nanoparticles were demonstrated to be active for the hydrogenation of allylbenzene derivatives (H<sub>2</sub> [4 atm], 20 °C, 3 h, 11 examples, 68-99% conversion), styrene derivatives (H<sub>2</sub> [30 atm], 20 °C, 12 h, 8 examples, 36-99% conversion) and diphenylacetylene derivatives (H<sub>2</sub> [4 atm], 45 °C, 16 h, 5 examples, 78-100% conversion) (Scheme 2.23). One example of a partial hydrogenation of diphenylacetylene to stilbene (78% conversion, Z:E = 3:1) was reported. The reaction tolerated tertiary amines, ethers, pyridyl, ester and acetal groups, however some reductive cleavage of ester functionalities was observed. In the case of chloro-substituted styrenes, competitive polymerisation decreased yields of the corresponding ethylbenzene derivatives.

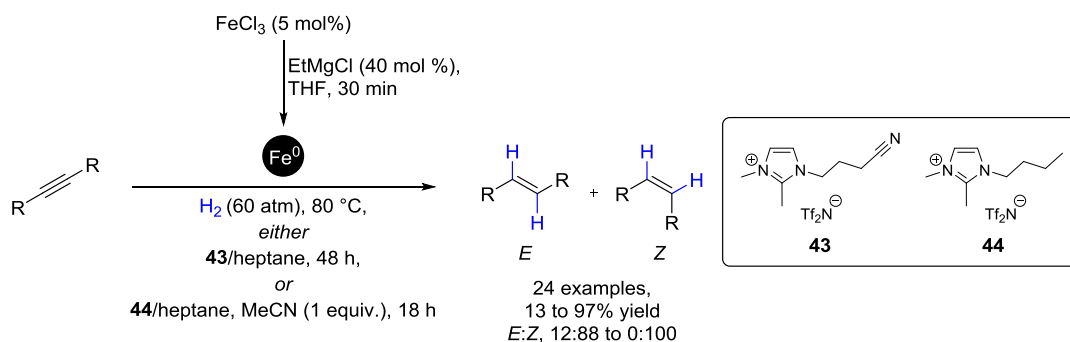
Optimisation of the reaction conditions produced two distinct systems: allylbenzene and diphenylacetylene derivatives were hydrogenated with an iron catalyst derived from  $\text{FeCl}_3$  and  $\text{EtMgCl}$  (5-6 equivalents); styrene derivatives were hydrogenated using an iron catalyst derived from  $\text{FeCl}_3$  and  $\text{EtMgCl}$  (2 equivalents). The properties of the nanoparticles formed in these reactions were investigated with X-ray absorption spectroscopy (XAS). X-ray absorption near edge structure (XANES) spectroscopy indicated that the former system exists as small  $\text{Fe}^0$  particles, while the later has partial  $\text{Fe}^0$  character (consistent with the stoichiometry of  $\text{EtMgCl}$ ). Extended X-ray absorption fine structure (EXAFS) spectroscopy indicated that reduction of  $\text{FeCl}_3$  with 6 equivalents of  $\text{EtMgCl}$  resulted in clusters of  $8 (\pm 2)$  Fe atoms, approximately 0.5 nm diameter, with each iron atom coordinated by 1 THF molecule. Reduction of  $\text{FeCl}_3$  with  $\text{EtMgCl}$  (2 equiv.) appeared to result in 3 iron atom aggregations, again coordinated by THF. No evidence was found in either case of Fe-Mg or Fe-Cl bonds. Unfortunately EXAFS spectroscopy is unable to detect Fe-H bonds meaning the existence of the proposed iron-hydride catalytic intermediates could not be confirmed or denied.

Given the similarities between this hydrogenation system, and one previously reported for cross-coupling of aryl Grignard reagents with alkyl- and vinyl- electrophiles,<sup>236</sup> the group of Jacobi von Wangelin produced a one-pot reductive cross-coupling.



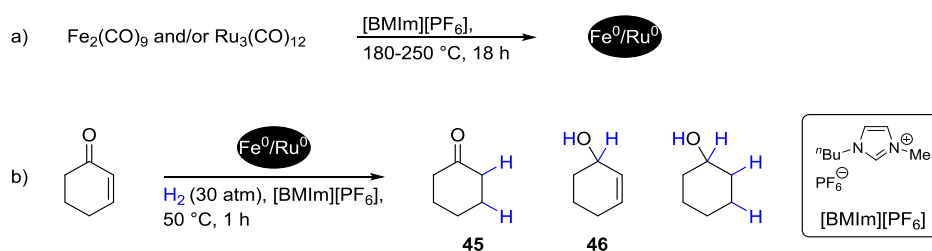
**Scheme 2.23** Conditions reported by the group of Jacobi von Wangelin for the *in situ* generation of iron(0) nanoparticles active for alkene and alkyne hydrogenation.<sup>89</sup>

The group of Jacobi von Wangelin have since utilised iron nanoparticles produced by the reduction of  $\text{FeCl}_3$  with  $\text{EtMgCl}$  for the (*Z*)-selective semi-hydrogenation of alkynes.<sup>237</sup> In order to effect the change in selectivity from complete hydrogenation to semi-hydrogenation, the solvent was changed from THF to either the nitrile-functionalised ionic liquid **43** or to a mixture of **44** and MeCN (Scheme 2.24). In the previous study, the catalyst solutions (in THF) were found to rapidly age and lose activity after 48 h. The ionic liquids proved to be excellent solvents, able to stabilise the catalytic species.<sup>238</sup>



**Scheme 2.24** *In situ* generation of iron(0) nanoparticles in ionic liquids for selective semi-hydrogenation of alkynes, reported by Jacobi von Wangelin.<sup>237</sup>

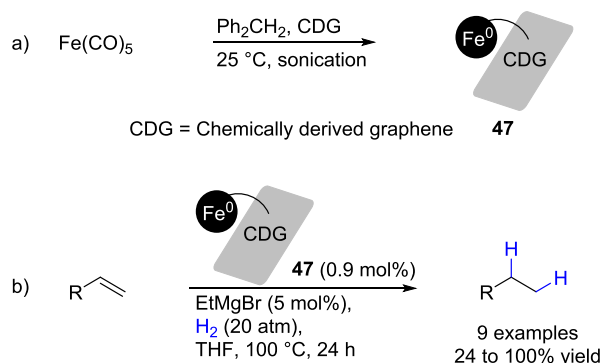
The Baiker group has synthesised iron and ruthenium mono- and bimetallic nanoparticles suspended in the ionic liquid [BMIm][PF<sub>6</sub>].<sup>239</sup> These nanoparticles were shown to be active for the hydrogenation of cyclohexenone to mixtures of cyclohexanone and cyclohexanol. The highest conversions (>94%) and least deactivation in recycling experiments were observed for the Ru<sup>0</sup> nanoparticles, however the cyclohexanone (**45**):cyclohexanol (**46**) ratio was only 5:1. Bimetallic 3:1 Fe:Ru and 1:1 Fe:Ru nanoparticles showed 72% and 91% conversions respectively and approximately 20:1 ratio of cyclohexanone:cyclohexanol. Further experiments demonstrated that the addition of supercritical CO<sub>2</sub> (60 atm) to the reaction mixtures dramatically increased the rate of reaction.



**Scheme 2.25** *Mixed bimetallic nanoparticles reported by the Baiker group: a) synthesis of Fe and Ru mono- and bimetallic nanoparticles in ionic liquids and b) and the use of Fe/Ru bimetallic nanoparticles for cyclohexenone hydrogenation.*<sup>239</sup>

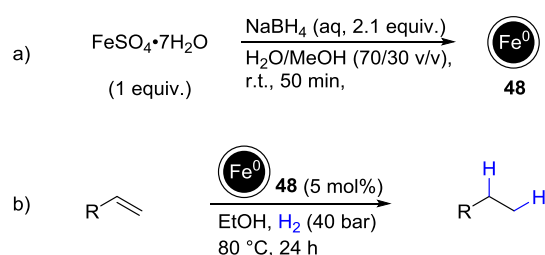
The group of Breit has developed iron(0) nanoparticles immobilised on to chemically derived graphene (CDG),<sup>240</sup> to produce a magnetically recoverable hydrogenation catalyst **47**.<sup>241</sup> The nanoparticles were produced by sonication of Fe(CO)<sub>5</sub>, had an average size of 4.37 ± 1.62 nm and represented 3.66 wt% loading on to the CDG sheets. The resultant material was active for alkene hydrogenation at 100 °C and H<sub>2</sub> (20 atm) in THF. The presence of EtMgCl (5 mol%) was required to activate the catalyst by reducing the surface oxide layer. The system was active for the hydrogenation of terminal alkenes and cyclic alkenes, but not for internal alkenes in unstrained systems or for tri- and tetra-substituted alkenes.





**Scheme 2.26** a) Synthesis of magnetically recoverable  $\text{Fe}^0$  nanoparticles and b) their use in alkene hydrogenation as reported by the group of Breit.<sup>241</sup>

Moore and co-workers have reported the synthesis of iron(0) nanoparticles **48** with an iron-oxide shell by the reduction of  $\text{FeSO}_4$  with  $\text{NaBH}_4$  in water/methanol mixtures.<sup>242,243</sup> The resulting iron-iron oxide core-shell nanoparticles (Fe CSNPs) had an average core diameter of  $44 \pm 8$  nm and a shell thickness of  $6 \pm 2$  nm and were 3.3 wt% boron. The resulting Fe CSNPs are active for the hydrogenation of alkyl-, aryl- and cyclic alkenes and terminal alkynes (5 examples, 82-100% yield) at  $80\text{ }^\circ\text{C}$  and 40 bar  $\text{H}_2$ . No hydrogenation of ketones was observed. The particles were successfully recycled, following evaporation of solvent and substrate, 8 times before loss of activity was observed. While the iron oxide layer appears to have decreased the reactivity compared to pure  $\text{Fe}^0$  nanoparticles, the core-shell particles were more stable towards aqueous conditions. Commercially available iron-iron oxide core-shell nanoparticles were also tested under the same conditions and found to be less reactive.

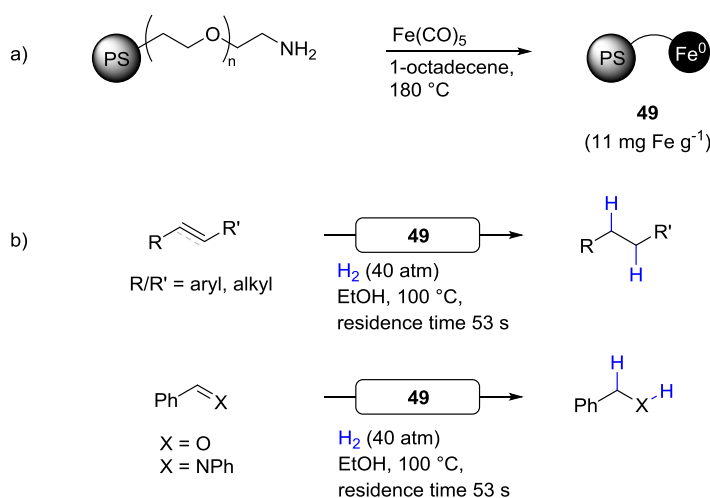


**Scheme 2.27** a) Iron/iron oxide CSNP synthesis, and b) the use of CSNP as an hydrogenation catalyst as reported by the group of Moore.<sup>242</sup>

Following on from these results, Moore and co-workers were inspired to design a more-active, air- and moisture stable  $\text{Fe}^0$  system. By supporting the  $\text{Fe}^0$  nanoparticles on amphiphilic polymer beads, the highly reactive iron species could be confined to hydrophobic pockets within the polymer, allowing reactions to be run in aqueous media.<sup>244</sup> Iron nanoparticles were deposited on to polystyrene beads, functionalised with polyethylene glycol linkers terminating with either: -

NH<sub>2</sub>, -COOH or -Br groups, by either by thermal treatment with Fe(CO)<sub>5</sub> (Scheme 2.28 a) or by the reduction of FeSO<sub>4</sub> with tea extract.<sup>140</sup> The highest loading, smallest particle size and least aggregation was observed for both methods of deposition in the -NH<sub>2</sub> functionalised polymers. Characterisation of the resulting resin by TEM revealed in both cases monodisperse Fe<sup>0</sup> nanoparticles ~5 Å diameter. ICP analysis revealed that thermal decomposition of Fe(CO)<sub>5</sub> produced a functionalised polymer **49** 1.17 wt% Fe<sup>0</sup>. Deposition of Fe<sup>0</sup> on to the same polymer by chemical reduction of FeSO<sub>4</sub> gave a material 0.26 wt% Fe<sup>0</sup>.

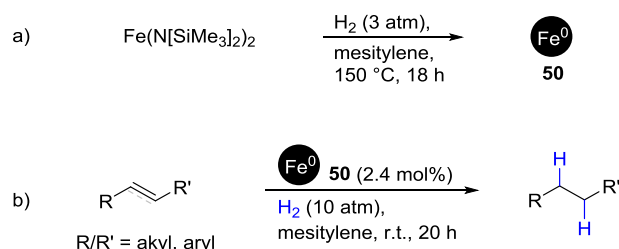
These functionalised polymers were used for catalytic hydrogenation of styrene in ethanol in both batch conditions and an H-cube<sup>®</sup> Continuous Flow Hydrogenation Reactor. Perhaps due to the extremely high local concentrations of catalyst within the reactor cell, both the thermally deposited catalyst and the one produced by the tea extract method were much more active in flow than in batch. The substrate scope of the hydrogenation was investigated, at 100 °C in superheated ethanol, 40 atm H<sub>2</sub>, residence time 53 s, using the iron-functionalised polymer produced by thermal decomposition (**49**) as a catalyst (Scheme 2.28 b). Aryl- alkenes were hydrogenated in good yield (4 examples, 84-100% yield), as were alkyl- (1,1- and 1,2-disubstituted) alkenes (5 examples, 14-90% yield) and alkyl alkynes (2 examples, 67-79% yield). Aryl- aldehydes and aldimines were also reduced (3 examples, 35-100% yield) while ketones esters, nitro, aryl-chlorides and aliphatic aldehyde and aldimine functionalities were unreactive.



**Scheme 2.28** a) Polymer supported iron(0) nanoparticles **49** synthesised by the group of Moores and b) their activity as hydrogenation catalysts.<sup>244</sup>

Lacroix *et al.* were able to produce and monodisperse Fe<sup>0</sup> nanoparticles **50** stabilised with HN(Si[CH<sub>3</sub>]<sub>3</sub>)<sub>2</sub> (HMDS) by the decomposition of (FeN[Si{CH<sub>3</sub>}]<sub>3</sub>)<sub>2</sub> at 150 °C under H<sub>2</sub> (3 bar) for 12 h (Scheme 2.29 a).<sup>142</sup> These nanoparticles were described as ‘ultrasmall’ (1.5 ± 0.2 nm) despite being considerably larger than those reported by Jacobi von Wangelin and co-workers

(~0.5 nm, *vide supra*). Nanoparticles produced in this manner were shown by Beller and co-workers to be active for the hydrogenation of terminal- and 1,2 disubstituted alkyl- and aryl-alkenes (11 examples, 87-99% yield, Scheme 2.29 b) at room temperature, under H<sub>2</sub> (10 atm).<sup>245</sup> Under the same conditions alkynes were also readily hydrogenated (8 examples, 88-99% yield).



**Scheme 2.29** a) 'Ultrasmall' iron(0) nanoparticles **50** reported by the group of Beller as b) alkene and alkyne hydrogenation catalysts.<sup>245</sup>

### 2.2.2.5 Iron-Catalysed Alkene and Alkyne Formal Hydrogenations

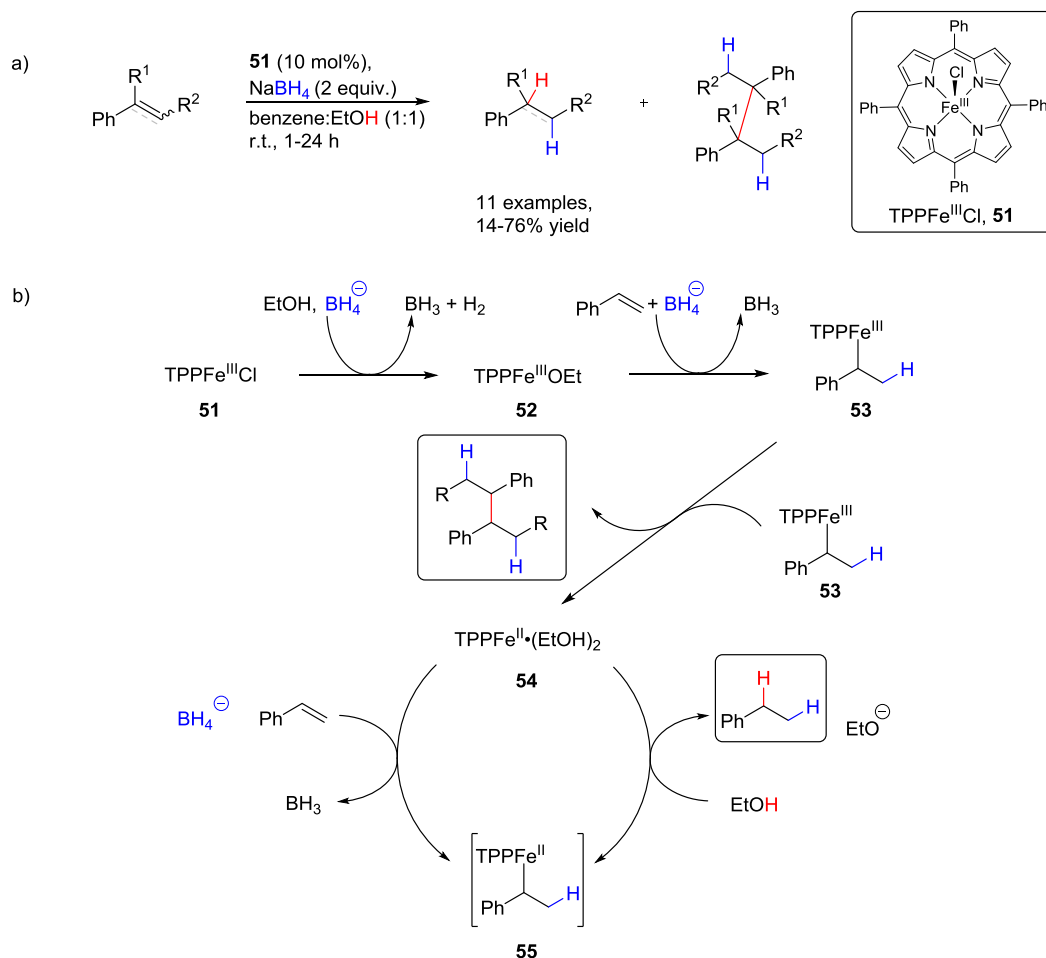
Iron-catalysed formal hydrogenation reactions typically use reductants that are not suitable for the uncatalysed reduction of alkenes and alkynes, and activate them in such a manner as to make them viable reductants. Due to the presence of strong reductants in the reaction mixture, it can be hard to gain insight into the mechanism of activation or the nature of the catalytically active species.

Ashby was able to produce transition-metal hydrides by the treatment of transition metal halides; TiCl<sub>3</sub>, CrCl<sub>3</sub>, FeCl<sub>2</sub>, FeCl<sub>3</sub>, CoCl<sub>2</sub>, and NiCl<sub>2</sub> with LiAlH<sub>4</sub>. The resulting hydride species were able to reduce stoichiometric quantities of alkyl- and aryl- alkenes to the corresponding alkane.<sup>246,247</sup> The proposed transition-metal halide species were also active for the reduction of alkynes. By careful reaction monitoring and quenching at the appropriate time, phenylacetylene could be reduced by LiAlH<sub>4</sub> and FeCl<sub>2</sub> to either styrene or ethylbenzene selectively.

Kano and co-workers communicated a report of the reduction of styrene by a tetraphenylporphyrinato-iron(III) complex TPPFe<sup>III</sup>Cl **51** and NaBH<sub>4</sub> in anaerobic organic solvents (Scheme 2.30 a).<sup>248,249</sup> The products of this reduction were ethylbenzene and *meso*- and ( $\pm$ )-2,3-diphenylbutane. In aprotic solvents, the only identifiable products were the reductively dimerised 2,3-diphenylbutane derivatives; the formation of ethylbenzene required protic solvents. This result, in conjunction with deuterium incorporation experiments using C<sub>2</sub>H<sub>5</sub>OD and NaBD<sub>4</sub>, showed that the proton at the  $\alpha$ -position of ethyl benzene was incorporated from solvent, and that at the  $\beta$ -position came from the borohydride reagent.

Following these labelling studies, UV spectroscopy and reactions under strictly air- and moisture sensitive conditions, the group of Kano came to propose the following mechanism (Scheme

2.30 b). The alkene-dimerisation product was proposed to be formed as part of the catalyst activation mechanism, in which: the ethoxide substituted  $\text{TPPFe}^{\text{III}}$  complex **52** was rapidly formed in solution, presumably with concurrent liberation of  $\text{H}_2$  gas. This could then perform a formal hydrometallation with an equivalent each of styrene and  $\text{BH}_4$  to produce the  $\sigma$ -alkyliron(III) complex **53**. Elimination of alkyl-radicals from two equivalents of this species results in the formation of alkyl- dimers and the formation of  $\text{TPPFe}^{\text{II}}$  complexes. The resulting  $\text{Fe}^{\text{II}}$  complex **54** is then catalytically active for the alkene hydrogenation *via* the  $\sigma$ -alkyliron(II) complex **55**, although the manner in which the reaction turned-over was not specified.

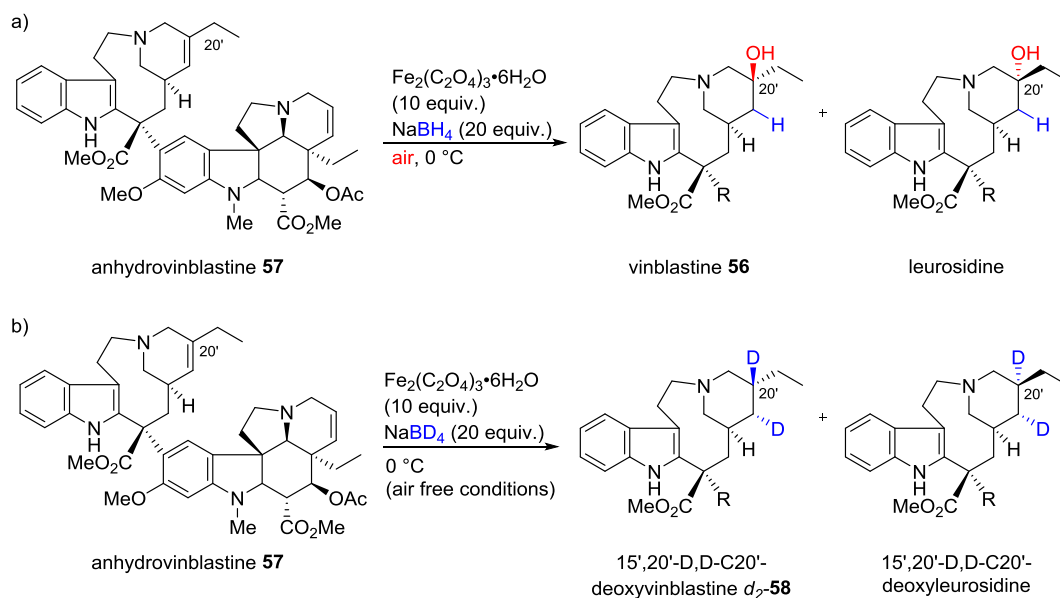


**Scheme 2.30** a)  $\text{TPPFe}^{\text{III}}\text{Cl}$  **51** catalysed hydrogenation of styrene derivatives reported by Kano, and  
b) the proposed mechanism thereof.<sup>249</sup>

Porphyrinato-iron complexes have also been used, in conjunction with  $\text{NaBH}_4$ , for the reduction of the  $\alpha,\beta$ -unsaturated esters to the corresponding saturated esters,<sup>250</sup> and the hydrofunctionalisation of alkenes with thiols and oxygen.<sup>251,252</sup>

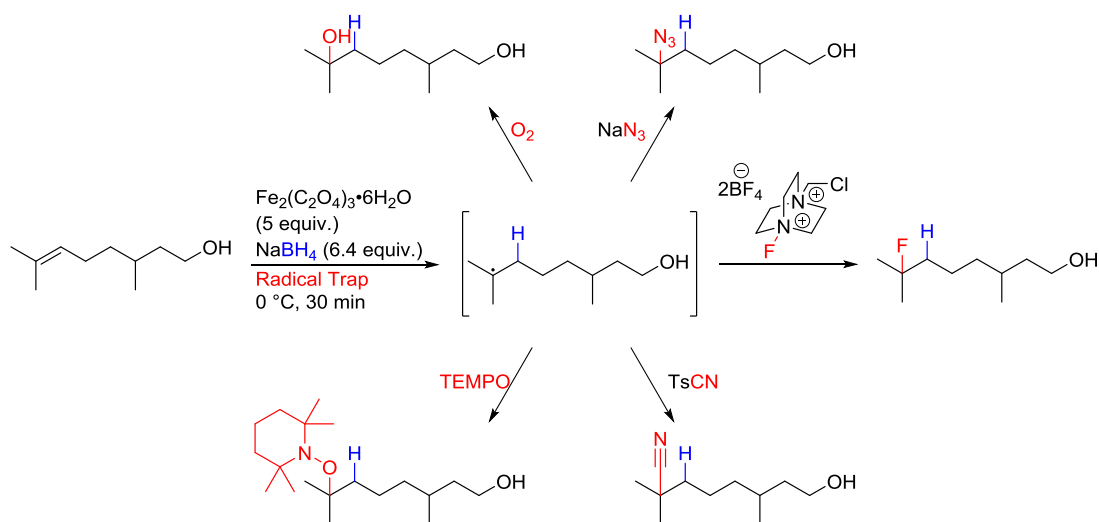
During studies towards the synthesis of vinblastine **56**,<sup>253</sup> Boger and co-workers produced an iron(III) oxalate and  $\text{NaBH}_4$  mediated, oxidation of anhydrovinblastine **57** (Scheme 2.31 a).<sup>116</sup>

Labelling studies showed the introduction of a proton from  $\text{NaBH}_4$  and incorporation of oxygen from air. Significantly under anaerobic conditions the same reaction produced C20'-deoxyvinblastine and its diastereomer C20'-deoxyleurosine by the selective reduction of the  $\Delta^{15'-20'}$ -double bond. The use of  $\text{NaBD}_4$  resulted in complete deuterium incorporation at both C15' and C20' to give  $d_2$ -**58** (Scheme 2.31 b).



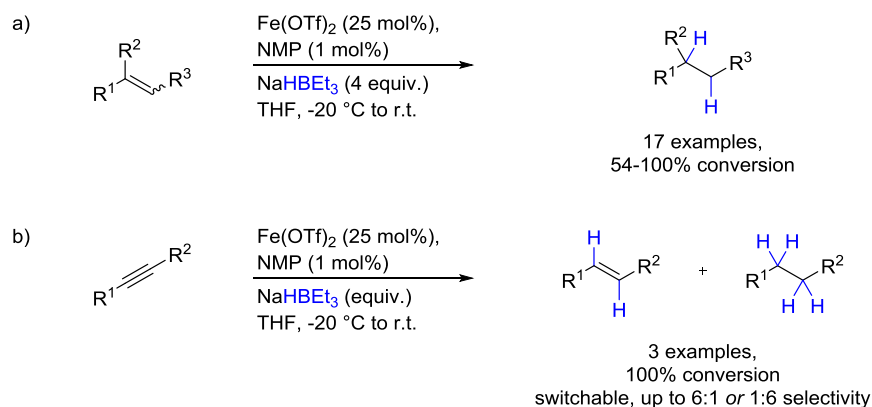
**Scheme 2.31** Boger's formal hydrogenation of alkenes using  $\text{Fe}_2(\text{ox})_3$  and  $\text{NaBH}_4$

A series of radical trap experiments allowed the production of vinblastine derivatives; functionalised at the C20' position with TEMPO, azido- and nitroso- groups. This protocol was later expanded to allow the radical mediated hydrofunctionalisation of various alkenes (Scheme 2.32).<sup>117,118</sup>



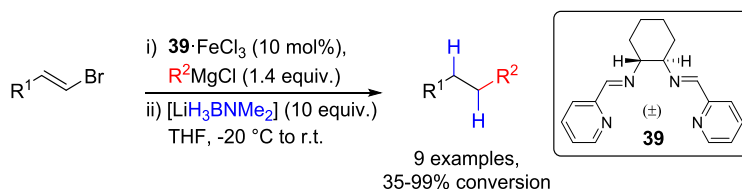
**Scheme 2.32** Use of iron(III) oxalate and NaBH<sub>4</sub> to mediate a formal alkene hydrofunctionalisation via tertiary alkyl- radicals.<sup>117,118</sup>

Thomas and co-workers have reported an iron-catalysed reduction of alkenes and alkynes using NaHBET<sub>3</sub> as the stoichiometric hydride source.<sup>254</sup> Using Fe(OTf)<sub>2</sub> (25 mol%), *N*-methyl-2-pyrrolidone (NMP, 1 mol%) and NaHBET<sub>3</sub> (4 equivalents) resulted in a system that is active for the formal hydrogenation of aryl- and alkyl- terminal alkenes (10 examples, 94-100% conversion), internal alkenes (4 examples, 54-100% conversion) and, significantly, trisubstituted alkenes (3 examples, 61-86% conversion) (Scheme 2.33 a). Disappointingly, an attempt to make this reaction enantioselective by the replacement of the NMP with enantiopure ligands was unsuccessful. Alkynes could also be reduced to a mixture of the partial- and complete hydrogenation product. By changing the quantity of NaHBET<sub>3</sub>, up to 6:1 selectivity for either product could be achieved (3 examples, complete conversion., Scheme 2.33 b). Deuterium labelling experiments showed that the both hydrogen atoms come exclusively from the hydride reagent.



**Scheme 2.33** Iron-catalysed,  $\text{NaHBEt}_3$  mediated, formal hydrogenation of a) primary, secondary and tertiary alkenes, and b) alkynes reported by the group of Thomas.<sup>254</sup>

The Thomas group has also exploited the common low-valent iron catalysts for cross-coupling reactions and reductions to report a sequential cross-coupling then hydride-mediated reduction.<sup>255</sup>  $\beta$ -halostyrene derivatives were coupled with aryl-, alkyl- and vinyl- magnesium chlorides in the presence of 10 mol% of iron(II) chloride and the tetra-dentate ligand (**39**); the resulting intermediate alkene was reduced by the addition of 10 equivalents of  $\text{LiH}_3\text{BNMe}_2$  (Scheme 2.34).  $\beta$ -Halo-4-chlorostyrenes were proto-dehalogenated on the aromatic ring, although the yields of the reductively cross-coupled product were still acceptable (2 examples, 60-66% yield). The homo-coupling of the  $\beta$ -halostyrene derivatives was also observed, and in the absence of the Grignard reagent gave full conversion to a mixture of the fully and partially reduced homo-dimer.

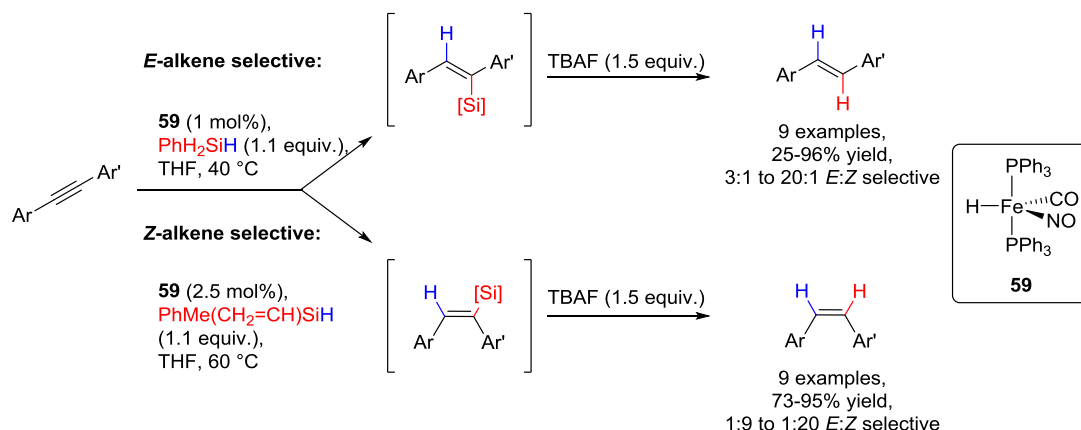


**Scheme 2.34** Reductive cross-coupling reactions reported by the group of Thomas.<sup>255</sup>

Hydrosilylation/protodesilylation protocols have been exploited by several groups to attain high stereoselectivity in formal semi-hydrogenation of alkynes to alkenes. While this strategy has a low atom economy, the high stereoselectivity of the initial hydrosilylation reaction leads to high selectivity in the products.

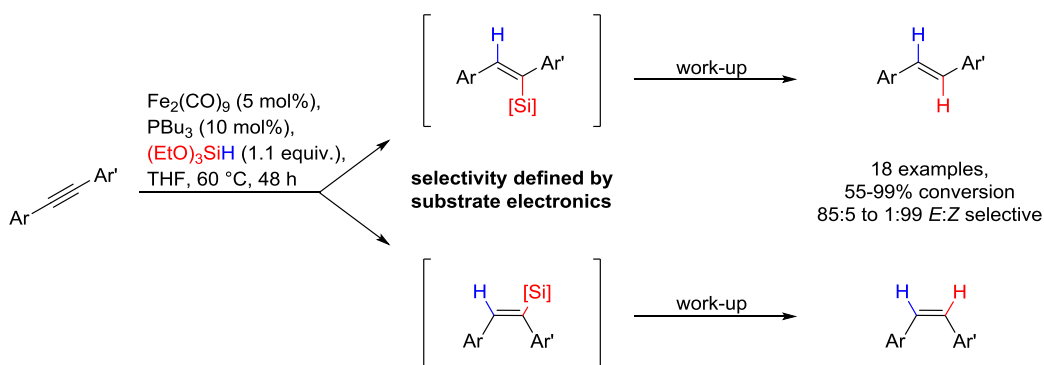
The group of Plietker has reported two protocols, both catalysed by the iron(0) phosphine complex **59**,<sup>256</sup> for the selective semi-hydrogenation of aryl-substituted alkynes to give the (*E*)-alkenes (9 examples, 25-96% yield, 3:1 to 20:1 *E:Z* ratio) and (*Z*)-alkene (9 examples, 73-95% yield, 1:9 to 1:20 *E:Z* ratio).<sup>257</sup> The stereoselectivity was determined by the steric bulk of the silane reagent:  $\text{PhSiH}_3$  gave the *trans*-addition product, which can be protodesilylated to give the

(*E*)-alkene; PhMe(CH<sub>2</sub>=CH)SiH gave the *cis*-addition adduct, leading to the (*Z*)-alkene. Alkyl-substituted alkynes gave only the *E*-alkene products independent of the silane source.



**Scheme 2.35** Pleitker's hydrosilylation/protodesilylation for selective alkyne reduction.<sup>257</sup>

Enthaler *et al.* reported the use of Fe<sub>2</sub>(CO)<sub>9</sub> (5 mol%) and PBu<sub>3</sub> (10 mol%) in the presence of (EtO)<sub>3</sub>SiH to perform the formal semi-hydrogenation alkynes (18 examples, 55-99% conversion, 85:5 to 1:99 *E*:*Z* ratio).<sup>258,259</sup> *E*/*Z* selectivity was determined largely by the electronic bias of the substituents on the alkyne.



**Scheme 2.36** Enthaler's hydrosilylation/protodesilylation protocol, leading to alkyne semi-hydrogenation, *E*:*Z* selectivity defined by substrate electronics.<sup>258,259</sup>

In conclusion, iron-catalysed alkene and alkyne formal hydrogenation reactions are a considerably less-well developed field than conventional iron-catalysed hydrogenation reactions. Consequently, these systems are also much less well understood.

## 2.3 PROJECT AIMS

Hydrogenation reactions catalysed by palladium species are used by research and synthetic chemists nearly universally for alkene reduction reactions.<sup>97</sup> Palladium-catalysed alkene hydrogenation reactions are popular because of the ubiquity of the catalyst and reagents, broad substrate scope, operational simplicity of the protocols and the robustness of the reaction. In

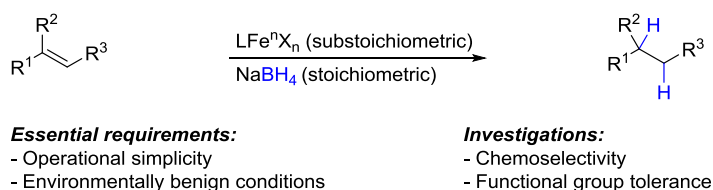


order to help shift chemistry to a more sustainable paradigm, hydrogenation reactions mediated by first-row transition metals, such as iron, need to match these qualities. In particular, for any iron-catalysed alkene hydrogenation to be widely used, there are several vital prerequisites: a pre-catalyst that is both commercially available and air- and moisture stable; an easy to handle stoichiometric reductant; and environmentally benign reaction conditions.

This project was conceived to develop an iron-catalysed alkene reduction that fulfils these requirements, by further development of previously reported work.  $\text{NaBH}_4$  was proposed as the preferred stoichiometric reductant, since it fulfils the requirements for the stoichiometric reductant: it is produced on thousands of tonnes scale annually, far more than any other boron hydride;<sup>260</sup> and it is a common laboratory reagent, that is both air- and moisture stable and easily handled.<sup>261</sup> Additionally,  $\text{NaBH}_4$  is well established as a stoichiometric reductant in Pd/C-catalysed formal hydrogenations, however these reactions are typically limited by a requirement for an additional stoichiometric additive such as acetic acid.<sup>95,262–264</sup>

$\text{NaBH}_4$  has been used in only a limited number of iron-catalysed alkene hydrogenation reactions, notably the porphyrin catalysed work of Kano,<sup>248,249</sup> and the superstoichiometric iron oxalate mediated reactions reported by Boger.<sup>116</sup> The first of these examples has limited ‘green chemistry’ credentials due to the use of an ethanol/benzene mixture for solvent, a high molecular weight catalyst and the generation of substantial quantity of an alkene dimerisation side-product. The second is similarly limited by the requirements for superstoichiometric quantities of iron, and a large excess of  $\text{NaBH}_4$ .

More reactive boron and aluminium hydride sources have also been used by both the Thomas group,<sup>254,255</sup> and others,<sup>81</sup> however these are much more reactive, are often pyrophoric and in some cases generate flammable and harmful gasses. This prevents use outside of strictly air- and moisture-sensitive conditions in laboratories hindering widespread adoption of the protocols.



**Scheme 2.37** Project aims: an operationally simple, environmentally benign formal hydrogenation of alkenes.

Therefore, the aims of this project were to develop an operationally simple, environmentally benign, and inexpensive formal hydrogenation of alkenes. This reaction utilised an air- and

moisture stable iron pre-catalyst and use a readily available, bench-stable reducing agent, ideally sodium borohydride.

## 2.4 RESULTS AND DISCUSSION

### 2.4.1 CATALYST IDENTIFICATION

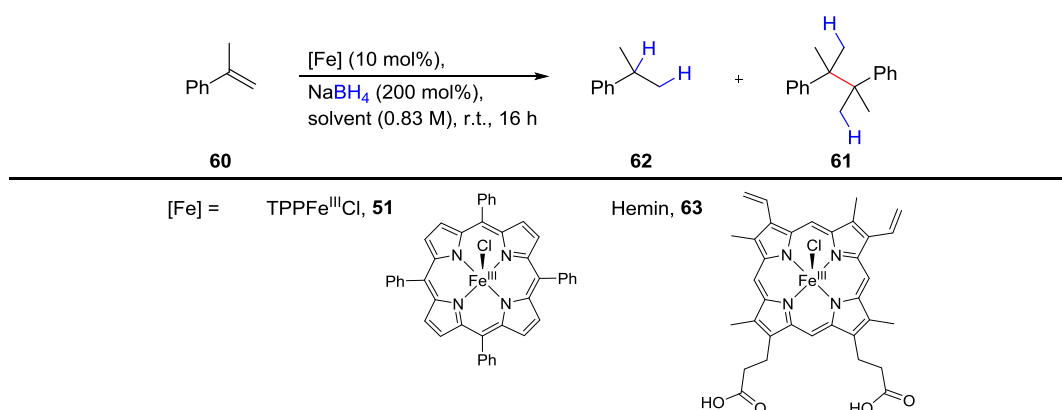
#### 2.4.1.1 Preliminary Work

Given the success of the Kano system for alkene hydrogenation using  $\text{NaBH}_4$ , initial work focused on the use of iron(III) porphyrin complexes to try and optimise an environmentally benign protocol for the formal hydrogenation of alkenes.

As reported by Kano,  $\text{TPPFe}^{\text{III}}\text{Cl}$  **51** is catalytically active for the formal hydrogenation of *a*-methylstyrene **60** in a range of mixed aromatic/alcoholic solvents, however the major product is the reductive dimerisation product **61**, not alkane **62** (Table 2.4-1, Entries 1-4).<sup>249</sup> Hemin **63** is a biologically derived iron(III) porphyrin species that is inexpensive and readily commercially available. Hemin demonstrated similar reactivity to that observed with  $\text{TPPFe}^{\text{III}}\text{Cl}$  (Table 2.4-1, Entries 5-8).

In all cases using the iron(III) porphyrin complexes, the work was plagued with low isolated yields and difficult work-ups due to the miscibility of the reaction mixture with the aqueous media added to perform extractions.

**Table 2.4-1 Use of TPPFeCl 51 and Hemin 63 for the formal hydrogenation and/or reductive dimerisation of  $\alpha$ -methylstyrene using  $\text{NaBH}_4$ .<sup>a</sup>**

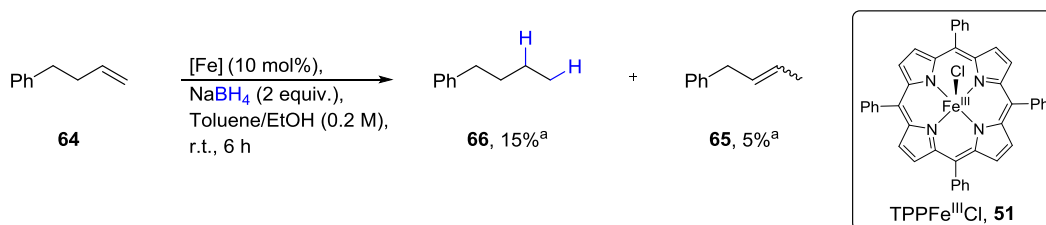


Entry	[Fe]	Solvent	Conversion (%) <sup>b</sup>	
			Hydrogenation Product <b>62</b>	Reductive Dimerisation Product <b>61</b>
1	TPPFe <sup>III</sup> Cl <b>51</b>	Toluene/MeOH	<b>10</b>	90
2	TPPFe <sup>III</sup> Cl <b>51</b>	Benzene/MeOH	<b>36</b>	64
3	TPPFe <sup>III</sup> Cl <b>51</b>	Toluene/EtOH	<b>2</b>	95
4	TPPFe <sup>III</sup> Cl <b>51</b>	Benzene/EtOH	intractable mixture of products	
5	Hemin <b>63</b>	Toluene/MeOH	-	90
6	Hemin <b>63</b>	Benzene/MeOH	<b>19</b>	54
7	Hemin <b>63</b>	Toluene/EtOH	<b>3</b>	83
8	Hemin <b>63</b>	Benzene/EtOH	-	94

<sup>a</sup>Conditions:  $\alpha$ -methylstyrene (0.2 mmol) in a solvent mixture (1:1 v/v, 0.2 M) was added to an iron(III) porphyrin species (10 mol%) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in GCMS and <sup>1</sup>H NMR spectroscopy. Typical isolated material from these reactions represents *circa* 30% of the starting material.

Given that styrene derivatives represent only a limited pool of substrates within the greater chemical space of alkenes, an alternative ‘standard’ substrate was sought. The requirements for the standard substrate were: having an alkene, not in conjugation with another  $\pi$ -system; sufficient molecular weight to be readily isolated; easily handled and readily tracked by both <sup>1</sup>H NMR and GCMS. 4-Phenyl-1-butene **64** fulfilled these requirements and so was used from hereon in as a test substrate for catalyst identification and development of the methodology.

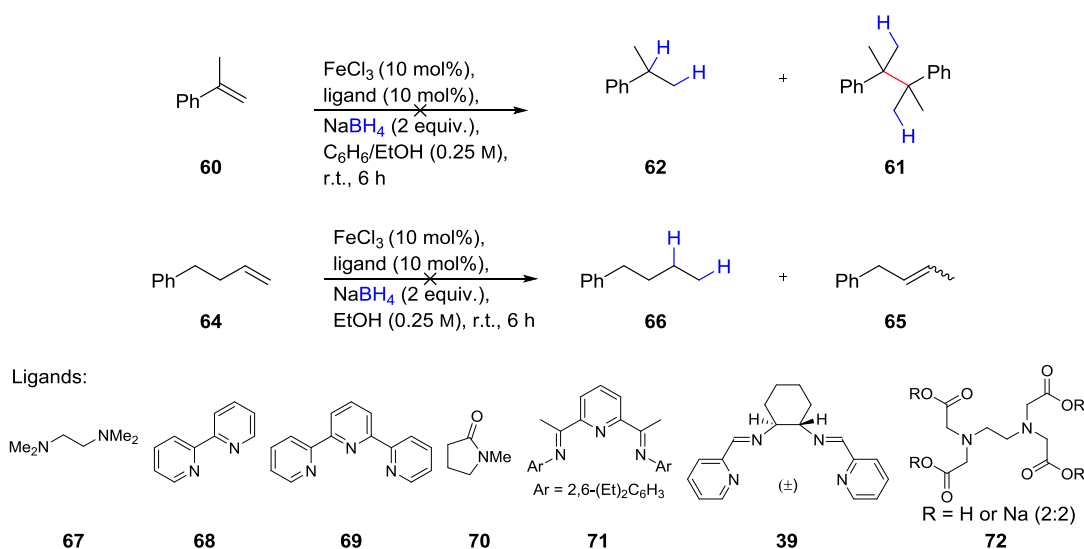
Disappointingly, very little hydrogenation of 4-phenyl-1-butene was observed using TPPFe<sup>III</sup>Cl in this system either. The reductive dimerization product was not observed using this system, presumably due to the lack of aromatic stabilisation of the requisite alkyl- radical intermediate. Mixtures of the alkene isomerisation product *cis/trans* 4-phenyl-2-butene **65** were obtained in addition to the hydrogenation product **66**.



**Scheme 2.38** Attempted formal hydrogenation of 4-phenyl-1-butene **64** with TPPFe<sup>III</sup>Cl **51** and NaBH<sub>4</sub>.

<sup>a</sup>Conversions measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy and GCMS. Typical isolated material from these reactions represents circa 30% of the starting material.

Due to the large quantities of side products, poor overall yields and intractable reaction mixtures alternative catalysts were sought. Screening of multidentate N-donor ligands along with FeCl<sub>3</sub> was performed to try and identify an active catalyst for the formal hydrogenation of alkenes. Screening FeCl<sub>3</sub> along with TMEDA **67**, BIPY **68**, TERPY **69**, NMP **70**, <sup>Et</sup>BIP **71**, tetradentate ligand **39** and EDTA **72** resulted in no systems capable of mediating the formal hydrogenation of either  $\alpha$ -methylstyrene or 4-phenyl-1-butene (Scheme 2.39).



**Scheme 2.39** Screen of N-donor ligands for the iron-catalysed alkene formal-hydrogenation with NaBH<sub>4</sub>. All examples returned <5% hydrogenation.

#### 2.4.1.2 Methodology Development

At this point, the further simplification of the attempted formal hydrogenation of alkenes was sought, therefore iron salts, in the absence of any ligands, were investigated as potential catalysts.

In order to identify iron species able to mediate the formal hydrogenation of 4-phenyl-1-butene **64** to phenylbutane **66**, stoichiometric amounts of iron(III) salts in the presence of NaBH<sub>4</sub> were

used. Iron(III) chloride, bromide and triflate (1 equivalent), in the presence of NaBH<sub>4</sub>, gave good reduction yields (Table 2.4-2, Entries 1-8). Additionally it was found that more than 1 equivalent of NaBH<sub>4</sub> was required for successful reduction. A small amount of isomerisation to the internal alkene **65** (up to 9%) was also observed.<sup>265</sup> Interestingly (3-chlorobutyl)benzene **73** and (3-bromobutyl)benzene **74** were obtained as side-products in up to 28% conversion when FeCl<sub>3</sub> and FeBr<sub>3</sub>, respectively, were used. This was presumably as a result of alkyl- radical formation, followed by halide abstraction from the iron salt.<sup>113–115,266</sup> With Fe(OTf)<sub>3</sub>, abstraction of the non-nucleophilic counter-ion was not observed. Additionally, reaction monitoring by <sup>1</sup>H NMR spectroscopy revealed that Fe(OTf)<sub>3</sub> gave phenylbutane in the shortest reaction times.

**Table 2.4-2 Screen of stoichiometric iron(III) salts and NaBH<sub>4</sub> for the formal hydrogenation of reactions<sup>a</sup>**

Ph-CH2-CH2-CH=CH2 (64)  $\xrightarrow[\text{EtOH (0.25 M), r.t., 16 h}]{\text{FeX}_3 (100 \text{ mol\%}), \text{NaBH}_4 (\text{equiv.})}$ 
Ph-CH2-CH2-CH2-CH3 (66) + Ph-CH2-CH=CH-CH3 (65) + Ph-CH2-CH2-CH(X)-CH3 (73, X = Cl; 74, X = Br)

Entry	Iron Salt	NaBH <sub>4</sub> (equiv.)	Time to Complete Conversion (min)	Hydrogenation product (66)	Yield (%) <sup>b</sup> Isomerisation product (65)	Halogenation product (73 or 74)
1	FeCl <sub>3</sub>	2	n.a.	15	2	28
2	FeCl <sub>3</sub>	3	90	50	3	25
3	FeCl <sub>3</sub>	4	n.a.	64	2	24
4	FeBr <sub>3</sub>	2	n.a.	42	1	14
5	FeBr <sub>3</sub>	3	n.a.	59	2	12
6	Fe(OTf) <sub>3</sub>	1	n.a.	19	3	0
7	Fe(OTf) <sub>3</sub>	2	<15	91	9	0
8	Fe(OTf) <sub>3</sub>	3	<15	93	7	0

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to an iron(III) salt (1.0 equiv.) and sodium borohydride, r.t., 18 h. <sup>b</sup>Yield measured by <sup>1</sup>H NMR spectroscopy of the crude reaction product using 1,3,5-trimethoxybenzene as internal standard.

Given the success of the reactions using stoichiometric iron salts, a screen of substoichiometric quantities (10 mol%) of iron(III) salts and 2 equivalents of NaBH<sub>4</sub> for the formal hydrogenation of 4-phenyl-1-butene **64** was performed. As observed in the stoichiometric reactions, iron(III) chloride, bromide and triflate all gave good yields of phenylbutane (Table 2.4-3, Entries 3-6). The catalytic activity of iron was attested to by high purity FeCl<sub>3</sub> (>99.99%) showing equal catalytic activity (Entry 4) to the reagent grade salts.<sup>267</sup> Iron(III) tosylate was also active for the hydrogenation in 75% yield (Entry 7). In all cases where good yields of phenylbutane was achieved, alkene isomerisation in up to 9% yield was again observed. The halogenation side reaction to give **73** or **74**, previously observed in the reductions with stoichiometric iron, were found to be considerably suppressed in the reactions using substoichiometric iron salts. Iron(III) nitrate, sulphate, phosphate, citrate, acetate and acac (Entries 8-12) gave low or zero conversion

to phenylbutane. Iron(III) salts with strongly coordinating -F (Entries 1 and 2) and -O (Entries 13 and 14) ligands were largely insoluble and unreactive.

**Table 2.4-3 Screening of iron(III) salts with NaBH<sub>4</sub> for the formal hydrogenation of 4-phenyl-1-butene<sup>a</sup>**

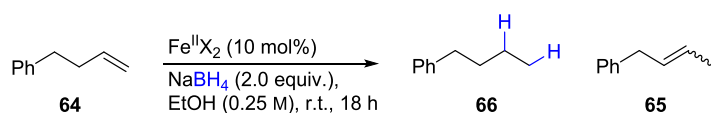
Entry	Iron Salt	Conversion (%) <sup>b</sup>	
		Hydrogenation product (66)	Isomerisation product (65)
1	FeF <sub>3</sub>	0	0
2	FeF <sub>3</sub> ·3H <sub>2</sub> O	3	0
3	FeCl <sub>3</sub>	91	5
4	FeCl <sub>3</sub> (>99.99%) <sup>c</sup>	89	6
5	FeBr <sub>3</sub>	90	9
6	Fe(OTf) <sub>3</sub>	90	10
7	Fe(OTs) <sub>3</sub>	75	8
8	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	17	0
9	FePO <sub>4</sub> ·4H <sub>2</sub> O	0	0
10	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·6H <sub>2</sub> O	0	0
11	Fe(acac) <sub>3</sub>	0	0
12	Fe <sup>III</sup> (C <sub>6</sub> H <sub>5</sub> O <sub>7</sub> )	0	0
13	Fe <sub>2</sub> O <sub>3</sub>	29	0
14	Fe(OH)O	0	0
15	K <sub>3</sub> Fe(CN) <sub>6</sub>	6	0

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to an iron(III) salt (10 mol%) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy. <sup>c</sup>High purity FeCl<sub>3</sub> used (>99.99% purity).

The screen of iron salts was then extended to include a variety of iron(II) salts (Table 2.4-4). As with the iron(III) salts, iron(II) salts bearing halide ligands gave the highest yields of phenylbutane (Entries 3-5). In general, lower yields were observed using iron(II) than the corresponding iron(III) pre-catalyst. Given that iron(II) salts are both more expensive and less reactive under these conditions than the iron(III) equivalent, none were carried forwards for further optimisation.

A second screen of 13 iron(III) salts (Table 5.3-1) and 14 iron(II) salts (Table 5.3-2) with NaBH<sub>4</sub> in EtOH for the hydrogenation of *trans*- $\beta$ -methylstyrene resulted in no systems that were competent for the reduction of 1,2-disubstituted alkenes (see Experimental for further details). This largely explains the isomerisation results observed in the hydrogenation of 4-phenyl-1-butene, whereby any  $\beta$ -hydride elimination from the proposed alkyl-iron intermediate will result in a species inert to the reaction conditions.

**Table 2.4-4 Screening of iron(II) salts with NaBH<sub>4</sub> for the formal hydrogenation of 4-phenyl-1-butene<sup>a</sup>**



Entry	Iron Salt	Conversion (%) <sup>b</sup>	
		Hydrogenation product ( <b>66</b> )	Isomerisation product ( <b>65</b> )
1	FeF <sub>2</sub>	<b>3</b>	0
2	FeF <sub>2</sub> ·4H <sub>2</sub> O	<b>5</b>	0
3	FeCl <sub>2</sub>	<b>81</b>	14
4	FeBr <sub>2</sub>	<b>58</b>	8
5	FeI <sub>2</sub>	<b>54</b>	20
6	Fe(OTf) <sub>2</sub>	<b>11</b>	0
7	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	<b>41</b>	0
10	Fe(SO <sub>4</sub> ) <sub>2</sub>	<b>5</b>	0
12	Fe <sup>II</sup> (MoO <sub>4</sub> ) <sub>2</sub>	<b>3</b>	0
8	Fe(acac) <sub>3</sub>	<b>3</b>	0
9	Fe(OAc) <sub>3</sub>	<b>3</b>	0
11	Fe <sup>II</sup> (C <sub>2</sub> O <sub>4</sub> ) <sub>2</sub> ·2H <sub>2</sub> O	<b>5</b>	0
13	Fe <sup>II</sup> (C <sub>6</sub> H <sub>11</sub> O <sub>7</sub> ) <sub>2</sub> ·nH <sub>2</sub> O	<b>3</b>	0
14	K <sub>4</sub> Fe(CN) <sub>6</sub>	<b>6</b>	0
15	Cp* <sub>2</sub> Fe <sub>2</sub> (CO) <sub>4</sub>	<b>0</b>	0
16	Ferrocene	<b>10</b>	0

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to an iron(II) salt (10 mol%) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy.

Iron(III) triflate was chosen as the catalyst for optimisation for the formal hydrogenation of 4-phenyl-1-butene. An attempt to reduce the catalyst loading to 1 mol% gave considerably diminished yields, even after 48 h (Table 2.4-5, Entry 1). A screen of NaBH<sub>4</sub> loading was performed, and at 10 mol% Fe(OTf)<sub>3</sub> loading, the quantity of NaBH<sub>4</sub> could be lowered to 1.5 equivalents and the reaction time reduced to 6 hours, without decreasing reaction yield (Entry 4).

**Table 2.4-5 Reaction optimisation for the formal hydrogenation of 4-phenyl-1-butene using Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub><sup>a</sup>**

Ph-CH2-CH2-CH=CH2 (64)  $\xrightarrow[\text{EtOH (0.25 M), r.t., 6 h}]{\text{Fe(OTf)}_3 \text{ (mol\%)}, \text{NaBH}_4 \text{ (equiv.)}}$  Ph-CH2-CH2-CH2-CH3 (66) + Ph-CH2-CH=CH-CH3 (65)

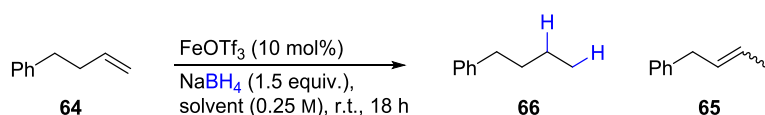
Entry	Fe(OTf) <sub>3</sub> loading (mol%)	NaBH <sub>4</sub> loading (equiv.)	Conversion (%) <sup>b</sup>	
			Hydrogenation product (66)	Isomerisation product (65)
1 <sup>c</sup>	1	2.0	47	7
2	10	0.5	26	-
3	10	1.0	19	4
4	10	1.5	90	10
5	10	2.0	91	8

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to Fe(OTf)<sub>3</sub> (10 mol%) and sodium borohydride (equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Conditions: 48 h.

Due to the low toxicity and availability from biomass of alcohols, they are considered to be 'green' solvents. Additionally, NaBH<sub>4</sub> is largely only soluble in polar solvents: water; alcohols and nitriles. Therefore a screen of these solvents was initiated (Table 2.4-6). Three different grades of ethanol were used: ethanol purified by distillation from Mg; 'absolute' ethanol (approx. 1% water); and ethanol in a 9:1 v/v mixture with water (Table 2.4-6, Entries 1-3). All three grades of ethanol were capable of supporting the alkene hydrogenation, although yields were strongly diminished in the presence of 10% water. Methanol, 1-butanol, 2-butanol and acetonitrile all proved to be poor reactions solvents (Entries 4-7). Due to the possibility that the protic alcohol solvent was responsible for the donation of at least one of the protons in the hydrogenation, the reaction was also performed in acetonitrile with ethanol (1 equivalent relative to alkene, Entry 8), this resulting in the recovery of starting material only. The sustainability and low toxicity of ethanol, along with the good reaction yields, made it the favoured reaction solvent.



**Table 2.4-6 Screening of solvents for the formal hydrogenation of 4-phenyl-1-butene using Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub><sup>a</sup>**



Entry	Solvent	Starting material (64)	Yield (%) <sup>b</sup> Hydrogenation product (66)	Isomerisation product (65)
1	EtOH <sup>c</sup>	-	<b>90</b>	10
2	EtOH <sup>d</sup>	-	<b>87</b>	10
3	EtOH (10% H <sub>2</sub> O)	-	<b>33</b>	4
4	MeOH	69	<b>12</b>	-
5	1-BuOH	2	<b>4</b>	13
6	2-BuOH	50	<b>5</b>	-
7	MeCN	67	<b>6</b>	3
8	MeCN <sup>e</sup>	71	-	-

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in a solvent (0.25 M) was added to Fe(OTf)<sub>3</sub> (10 mol%) and sodium borohydride (1.5 equiv.), r.t., 18 h. <sup>b</sup>Yield measured by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. <sup>c</sup>EtOH purified by distillation over Mg. <sup>d</sup>Commercially available 'absolute' EtOH. <sup>e</sup>EtOH (1 equiv.).

Other simple air-stable hydride sources, including PhSiH<sub>3</sub>, NaHB(CN)<sub>3</sub> and Hantzsch ester were screened for alkene hydrogenation in both the presence and absence of NaBH<sub>4</sub> (0.25 equivalents). However none of these systems proved to be capable of mediating the reduction of 4-phenyl-1-butene.

## 2.4.2 CONTROL REACTIONS

There are a considerable number of previous reports in which reactions were proposed to be catalysed by iron species, but in actual fact the iron pre-catalysts were acting as a reservoir for alternative catalytic species.<sup>109,267,268</sup> Of particular significance are the trace quantities of other metals such as copper, nickel or the noble-metals present in iron salts and the *in situ* generation of Brønsted acids.

Brønsted and Lewis acidic species were tested for catalytic activity in the optimised formal hydrogenation system (Table 2.4-7, Entries 1-3). Aluminium chloride, triflic acid and sodium triflate all proved to be completely inactive for the formal hydrogenation of 4-phenyl-1-butene. This suggests that neither 'hidden' Brønsted nor Lewis acid catalysis is responsible for the hydrogenation activity.

**Table 2.4-7 Screen of Bønsted and Lewis acids for activity in alkene formal hydrogenation with NaBH<sub>4</sub><sup>a</sup>**

Ph-CH2-CH2-CH=CH2 (64)  $\xrightarrow[\text{EtOH (0.25 M), r.t., 6 h}]{\text{Catalyst (10 mol\%), NaBH}_4 \text{ (2.0 equiv.)}}$  Ph-CH2-CH2-CH2-CH3 (66) + Ph-CH2-CH=CH-CH3 (65)

Entry	Pre-catalyst	Loading (mol%)	Yield (%) <sup>b</sup>	
			Hydrogenation product (66)	Isomerisation product (65)
1	AlCl <sub>3</sub>	10	4	0
2	HOTf	10	6	0
3	NaOTf	10	0	0

<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to an acid (10 mol%) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Yield measured by by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard.

In the absence of iron, no reduction of the alkene was observed. Additionally, high purity FeCl<sub>3</sub> (>99.99%) showed equal catalytic activity to standard commercially available material (*vide supra*, Table 2.4-3, Entry 4).

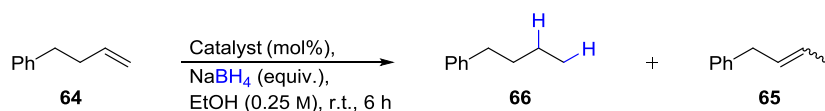
In order to distinguish whether the iron salts used in this alkene hydrogenation reaction were catalytically active in themselves or merely sources for another catalytically active metal species, the reaction mixtures were probed with inductively coupled plasma mass spectroscopy (ICP-MS) (Table 2.4-8). By a considerable margin, the largest impurities in the iron salt were aluminium species (c.a. 2% of the material analysed, although this varied considerably by sample). Gratifyingly, with the exception of silver, the noble metals (including Ru, Rh, Pd, Ir and Pt) were all present in Fe(OTf)<sub>3</sub> in 1 ppm or lower quantities, strongly suggesting that they are not responsible for the catalytic activity.

**Table 2.4-8 ICP-MS analysis of the relative abundance (ppm) of metals in Fe(OTf)<sub>3</sub><sup>a</sup>**

Al	Cr	Mn	Ni	Cu	Mo	Ru	Rh	Pd	Ag	Ir	Pt
18120	110	749	27	89	19	<1	<1	1	36	<1	<1

<sup>a</sup>Mean values of 3 different samples. Abundance recorded relative to the abundance of iron.

The chloride salts of the metal species (AgOTf was used rather than AgCl due to AgCl being largely inert and insoluble) that were found to be present in significant quantities were tested for catalytic activity in the absence of iron (Table 2.4-9). AlCl<sub>3</sub>, (*vide supra*) which is non-redox active, and therefore capable of acting only as a simple Lewis acid, was largely inactive under these conditions. AgOTf was also completely inert to these conditions. CuCl<sub>2</sub>, MnCl<sub>2</sub> and NiCl<sub>2</sub> all showed some activity when used at 10 mol% loading, but when used at the loadings found in the ICP-MS analysis were completely inactive.

**Table 2.4-9 Investigation into the role of metal impurities in Fe(OTf)<sub>3</sub><sup>a</sup>**

Entry	Pre-catalyst	Loading	Yield (%) <sup>b</sup>	
			Hydrogenation product ( <b>66</b> )	Isomerisation product ( <b>65</b> )
1	AgOTf	10 mol%	<b>2</b>	0
2	CuCl <sub>2</sub>	10 mol%	<b>54</b>	0
3	CuCl <sub>2</sub>	90 ppm	<b>0</b>	0
4	MnCl <sub>2</sub>	10 mol%	<b>11</b>	0
5	NiCl <sub>2</sub>	10 mol%	<b>80</b>	0
6	NiCl <sub>2</sub>	30 ppm	<b>0</b>	0

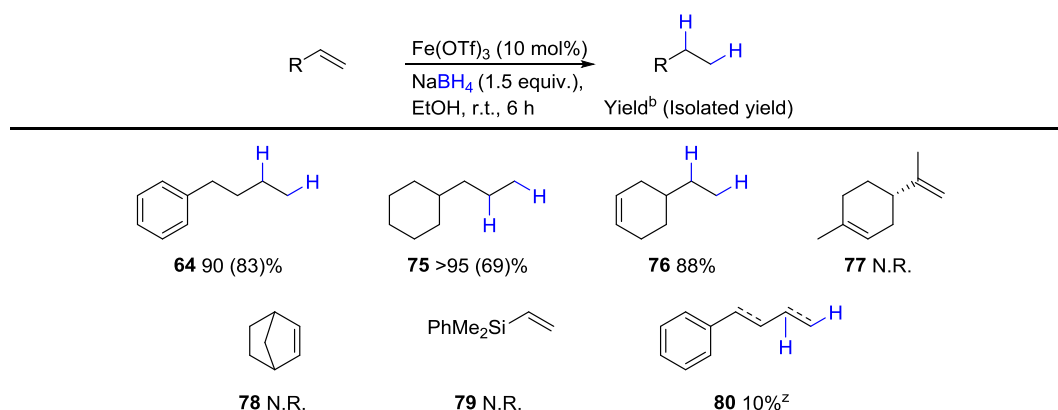
<sup>a</sup>Conditions: 4-phenyl-1-butene **64** (0.5 mmol) in ethanol (0.25 M) was added to a metal salt and sodium borohydride (1.5 equiv.), r.t., 6 h. <sup>b</sup>Yield measured by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard.

These results give confidence that the formal alkene hydrogenation is mediated by an iron catalyst generated *in situ* from Fe(OTf)<sub>3</sub>.

### 2.4.3 SUBSTRATE SCOPE

With the optimal conditions of Fe(OTf)<sub>3</sub> (10 mol%), NaBH<sub>4</sub> (1.5 equivalents) in ethanol (0.25 M), the substrate scope of the formal hydrogenation was investigated. Simple alkenes, such as 4-phenyl-1-butene **64** and allylcyclohexene were successfully hydrogenated in high yields to give alkanes **66** and **75** respectively (Table 2.4-10). 4-Vinylcyclohexene was selectively hydrogenated to give ethylcyclohexene **76**, demonstrating that the developed system was chemoselective for the reduction of terminal alkenes over internal alkenes. Neither the 1,2- nor 1,1-disubstituted alkene of (+)-limonene **77** underwent reduction under these conditions and even 1,2-disubstituted alkenes with considerable ring strain, such as norbornene **78**, were inert to these reaction conditions. Vinyltrimethylphenylsilane **79** was also unreactive under these conditions, presumably due to steric bulk proximal to the alkene. Submitting a diene, 1-phenyl-1,3-butadiene, to the developed reaction conditions resulted only in low yields (10%) of a mixture of hydrogenation products **80**.

**Table 2.4-10 Formal hydrogenation of non-functionalised alkyl-alkenes using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ <sup>a</sup>**



<sup>a</sup>Conditions:  $\text{Fe}(\text{OTf})_3$  (10 mol%) was added to an alkene (1.0 mmol) and  $\text{NaBH}_4$  (1.5 equiv.) in ethanol (0.25 M), r.t., 6 h. <sup>b</sup>Yields determined by integrals of starting material and product peaks in  $^1\text{H}$  NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. Values in parentheses are isolated yields following flash column chromatography. <sup>c</sup>Mixture of hydrogenation products observed.

Having determined that the  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$  system was highly active for the chemoselective formal hydrogenation of terminal alkenes, the functional-group tolerance of the reaction was investigated (Table 2.4-10). Fluoride- and chloride- substituted alkenes were reduced to the corresponding alkanes **81** and **82** in >90% yield, with no protodehalogenation.<sup>269</sup> Only in the case of 4-(4-bromophenyl)-1-butene was 18% of the protodehalogenated hydrogenation product **64** observed in addition to the hydrogenation product **83**. The perfluorinated alkene 1*H*,1*H*,2*H*-perfluoro-1-octene **84** was unreactive, presumably due to immiscibility in the reaction media.

Although the reduction was carried out in ethanol, inclusion of an alcohol or ketone in the alkene substrate diminished reduction yields: 1-decene-3-ol gave only 20% of the decane-3-ol **85**; and 1-(4-methylphenyl)-4-penten-1-ol gave the corresponding alkane **86** in poor yields. Interestingly, 1-(4-methylphenyl)-4-penten-1-one gave the same product **86**, as a result of ketone reduction (presumably by the background reactivity of  $\text{NaBH}_4$ ) in similarly poor yield. Cinchona alkaloids, such as quinine **87**, were completely unreactive under the developed reaction conditions.

Despite the lability of benzyl protecting groups under conventional hydrogenation conditions, both benzyl and silyl-ether protecting groups were conserved during alkene reduction giving alkenes **88** and **89** in 50% and 56% yield respectively. The rest of the mass balance consisted of unreacted starting material, with no deprotected material observed. The diminished yields were

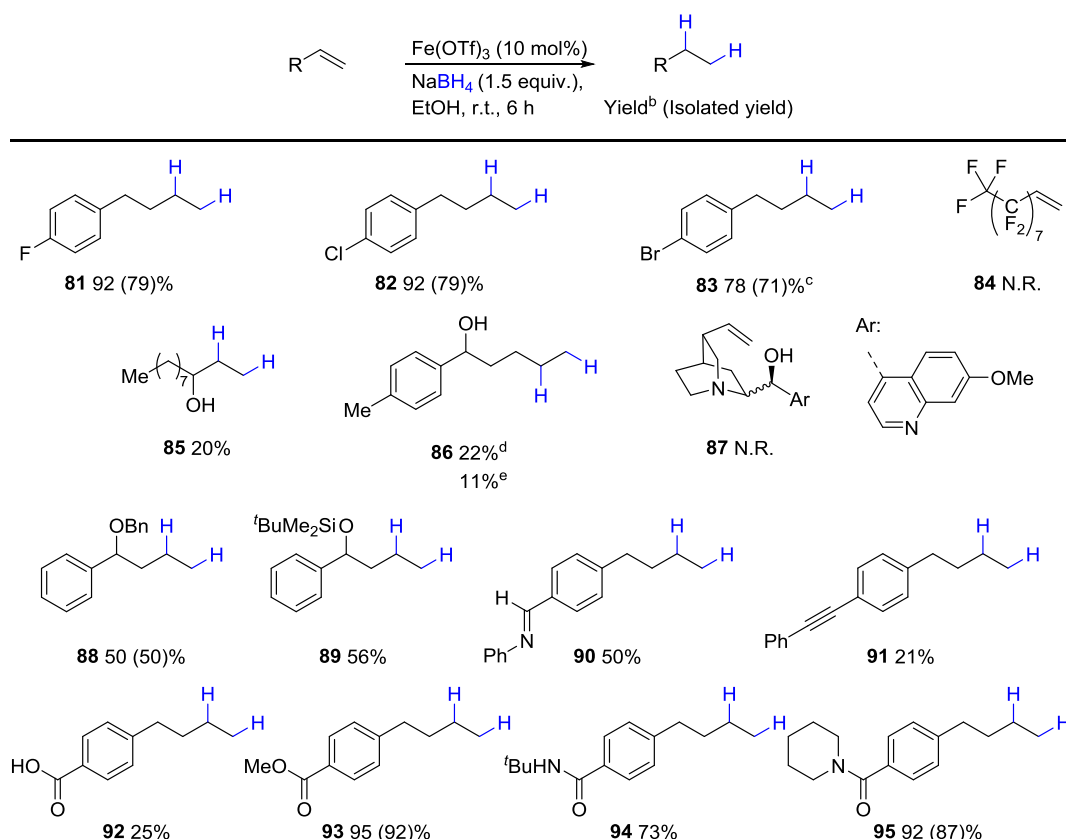
presumably due to the steric bulk proximal to the alkene. This demonstrates that protected alcohols can be successfully hydrogenated under these conditions.

An aldimine substituted alkane **90** could be generated in a synthetically useful yield of 50% without observable reduction of the imine.

An example of an alkene functionalised with an alkyne, was subjected to the reaction conditions, giving only 21% of the target alkane **91**. No evidence of alkyne reduction was observed.

An example of a carboxylic acid functionalised alkene was, surprisingly, successfully reduced to the corresponding alkane **92** albeit in only 25% yield. An ester functionalised terminal alkene was successfully hydrogenated to the corresponding alkane **93** in >90% isolated yield. Additionally, alkenes functionalised with primary and secondary amides were successfully reduced to **94** and **85** in good yields. No reduction or hydrolysis of the esters and amide functionality was observed despite previous reports of the reduction of esters and amides with NaBH<sub>4</sub> in MeOH.<sup>270,271</sup>

**Table 2.4-11 Formal hydrogenation of alkyl-alkenes bearing other functionality using Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub><sup>a</sup>**



<sup>a</sup>Conditions: Fe(OTf)<sub>3</sub> (10 mol%) was added to an alkene (1.0 mmol) and NaBH<sub>4</sub> (1.5 equiv.) in ethanol (0.25 M), r.t., 6 h. <sup>b</sup>Yields determined by integrals of starting material and product peaks in <sup>1</sup>H NMR relative to 1,3,5-trimethoxybenzene internal standard. Values in parentheses are isolated yields following flash column chromatography. <sup>c</sup>18% phenylbutane **57** also recovered. <sup>d</sup>Derived from 1-(4-methylphenyl)-4-penten-1-one. <sup>e</sup>Derived from 1-(4-methylphenyl)-4-penten-1-ol.

Styrene derivatives could be also successfully reduced; however longer reaction times and higher quantities of NaBH<sub>4</sub> were required and yields were generally lower than for the alkyl-alkenes (Table 2.4-12). Additionally, in all cases where successful hydrogenation was observed (and several cases when it was not), high depletion of the starting material was observed but with low yields of the hydrogenation product obtained and the formation of viscous reaction mixtures. Additionally, a broadening and flattening of peaks in <sup>1</sup>H NMR spectroscopy was observed, which is characteristic of a large number of similar chemical environments. These observations strongly imply polymerisation of the alkene starting material.

Alkyl-functionalised styrene derivative 4-*tert*-butylstyrene gave the corresponding alkane **96** in 45% isolated yield. 1,1- and 1,2-disubstituted styrenes **97** and **98** proved to be completely inert to the developed hydrogenation conditions. 4-Chlorostyrene was successfully reduced to the

corresponding alkane **100**, whereas the bromo- substituted equivalent gave both the hydrogenation product **101** and the protodehalogenation product phenylethane. 3-Trifluorostyrene was reduced to give the corresponding alkane **102** in 58% yield.

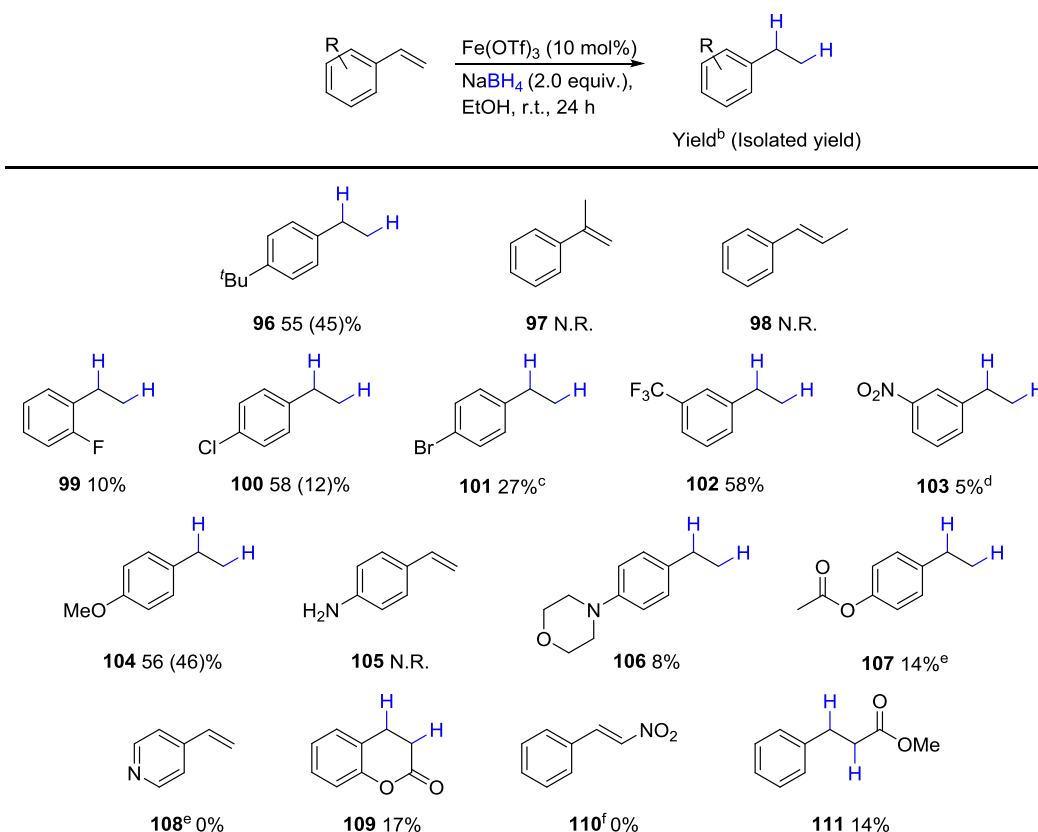
The formal hydrogenation of 3-nitrostyrene was of particular significance, since in addition to alkene hydrogenation to give **103**, a mixture of products originating from nitro group hydrogenation were also observed. This nitro group reduction as a competitive reaction with alkene hydrogenation led to a research project on nitro group hydrogenation (Chapter 3).

4-Methoxystyrene gave the corresponding hydrogenation product **104** in 56% yield. Primary and tertiary amine substituted styrene derivatives gave zero or poor yields of the hydrogenation products (**105** and **106**).

4-Vinylpyridine **108**, when subjected to the reaction conditions, gave only an intractable mixture of polymerisation products.

Coumarin could be reduced to dihydrocoumarin **109**, representing the first example of an internal alkene that could be hydrogenated under the developed conditions, albeit in only 17% yield. In light of the coumarin result other styrene derivatives bearing electron- withdrawing groups at the  $\beta$ -position were investigated.  $\beta$ -nitrostyrene **110** was completely unreactive, whereas  $\beta$ -methyl cinnamate gave the hydrogenation product in **111** in 14% yield. While it was interesting that internal alkenes could be reactive, in order to obtain synthetically useful yields, considerable optimisation would be required.

**Table 2.4-12 Formal hydrogenation of styrene derivatives using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ .<sup>a,b</sup>**



<sup>a</sup>Conditions:  $\text{Fe}(\text{OTf})_3$  (10 mol%) was added to a styrene derivative (1.0 mmol) and  $\text{NaBH}_4$  (2.0 equiv.) in ethanol (0.25 M), r.t., 18 h. <sup>b</sup>Yields determined by integrals of starting material and product peaks in  $^1\text{H}$  NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. Values in parentheses are isolated yields following flash column chromatography. <sup>c</sup>5% of phenylethane also isolated. <sup>d</sup>6% 3-aminostyrene **105** also observed. <sup>e</sup>Complete polymerisation of starting material observed. <sup>f</sup>Intractable mixture of products obtained.

In contrast to the work of de Vries using iron nanoparticles,<sup>86</sup> ethyl- and *tert*-butyl-acrylate could be chemoselectively reduced at the alkene to give **112** and **113** in 90-95% yield. Once again, incorporation of methyl groups at either the  $\alpha$ - or  $\beta$ -position on these substrates (**114** and **115**) resulted in little or no hydrogenation. Other electron deficient internal alkenes such as maleic anhydride **116** proved to be inert to the developed conditions. The diene **118** also proved to be unreactive. Dimethyl acrylamide **119** could be reduced to the corresponding alkane in 75% yield, however use of the protic substrate acrylamide **120** resulted in no hydrogenation.



**Table 2.4-13 Formal hydrogenation of acrylate- and acrylamide derivatives using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ .<sup>a</sup>**

$\text{R}-\text{CH}=\text{CH}_2 \xrightarrow[\text{EtOH, r.t., 6 h}]{\text{Fe}(\text{OTf})_3 (10 \text{ mol\%}), \text{NaBH}_4 (1.5 \text{ equiv.})}$		Yield <sup>b</sup> (Isolated yield)
		112 90%
		113 95 (73)%
		114 N.R.
		115 N.R.
		116 N.R.
		117 N.R.
		118 N.R.
		119 75%
		120 <sup>c</sup>

<sup>a</sup>Conditions:  $\text{Fe}(\text{OTf})_3$  (10 mol%) was added to an acrylate- or acrylamide derivative (1.0 mmol) and  $\text{NaBH}_4$  (1.5 equiv.) in ethanol (0.25 M), r.t., 6 h. <sup>b</sup>Yields determined by integrals of starting material and product peaks in  $^1\text{H}$  NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. Values in parentheses are isolated yields following flash column chromatography. <sup>c</sup>Intractable mixture of products obtained.

The attempted hydrogenation of 5-phenyl-1-butyne **121**, resulted only in a poor yields of the full hydrogenation product phenylpentane. The addition of a large excess of  $\text{NaBH}_4$  (20 equivalents) resulted in only 34% of the alkane product. Diphenylacetylene **122** was completely unreactive under these conditions. Additionally, the reduction of 4-phenyl-1-butene in the presence of 10 mol% diphenylacetylene resulted in a reduced yield of phenylbutane (15%) and no evidence of reduction of the diphenylacetylene. These results correspond with the reduction of alkene **91** (incorporating an alkyne functionality) which also proceeded poorly. Alkynes appear to strongly inhibit the hydrogenation reaction.

**Table 2.4-14 Formal hydrogenation of alkynes using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ .<sup>a,b</sup>**

$\text{R}-\text{C}\equiv\text{C}-\text{R} \xrightarrow[\text{EtOH, r.t., 6 h}]{\text{Fe}(\text{OTf})_3 (10 \text{ mol\%}), \text{NaBH}_4 (n \text{ equiv.})}$	
	121 7 <sup>c</sup> , 34 <sup>d</sup> %
	122 N.R.

<sup>a</sup>Conditions:  $\text{Fe}(\text{OTf})_3$  (10 mol%) was added to an alkyne (1.0 mmol) and  $\text{NaBH}_4$  (1.5 equiv.) in ethanol (0.25 M), r.t., 6 h. <sup>b</sup>Yields determined by integrals of starting material and product peaks in  $^1\text{H}$  NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. <sup>c</sup> $\text{NaBH}_4$  (1.5 equiv.). <sup>d</sup> $\text{NaBH}_4$  (20 equiv.).

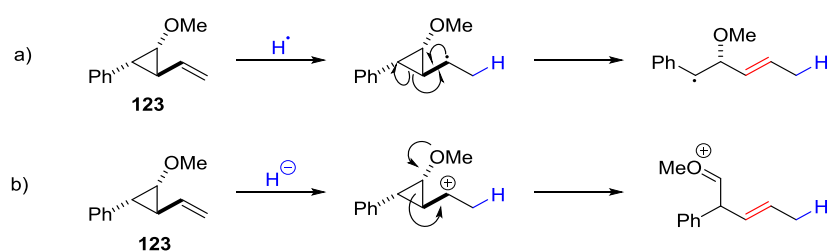
## 2.4.4 MECHANISTIC INVESTIGATIONS

As previously discussed, two contrasting mechanisms have been proposed for previously reported iron-catalysed,  $\text{NaBH}_4$ -mediated, alkene reductions (see Section 2.2.2.5). Kano proposed the addition of an iron-hydride to the alkene, followed by proton abstraction from ethanol.<sup>249</sup> In contrast, Boger and Thomas have proposed that both hydrogen atoms originated from borohydride species.<sup>116,254</sup> In the later mechanism it is not known whether the catalyst is a discrete species, or the surface of a solid or colloidal metal species. Additionally, it is not clear what species acts as the required electron-sink.

$\text{NaBH}_4$  has been shown to reduce iron (II/III) salts to a range of nanoparticulate or low oxidation-state iron and iron/boron species.<sup>137,138,141</sup> While the formation of nanoparticles cannot be ruled out, the lack of stabilisers or an induction period would appear to suggest against these being the active catalytic species.

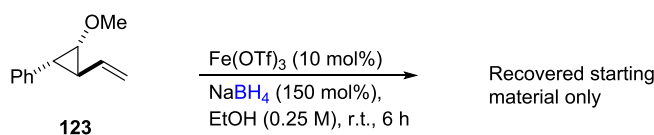
### 2.4.4.1 Investigations into Radical Intermediates

Given that previously reported iron-catalysed formal hydrogenation reactions using  $\text{NaBH}_4$  have proceeded by a radical mechanism, it was imperative to investigate this possibility. Firstly, the radical clock alkene **123** was investigated as a substrate for the iron(III) triflate catalysed formal hydrogenation. Alkene **123** contains a 1-phenyl,2-methoxy- functionalised cyclopropane ring that can undergo ring-opening reactions when radical or cationic intermediates are formed. Significantly, the electronic bias of the cyclopropane ring results in different ring opened products depending on the intermediate (Scheme 2.40), making **123** a powerful mechanistic probe.<sup>272,273</sup>



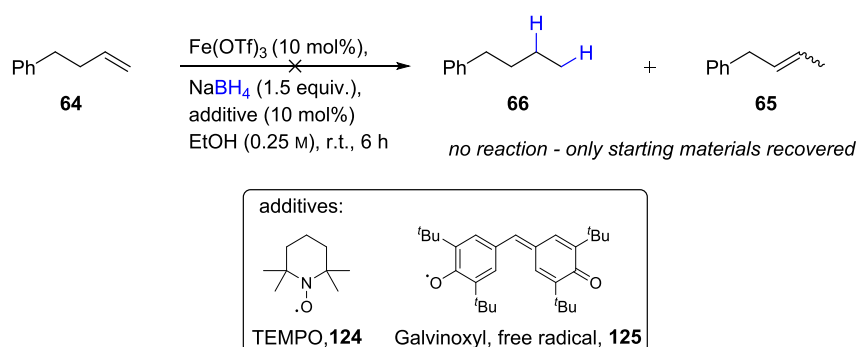
**Scheme 2.40** General scheme of cyclopropane ring-opening reactions of radical-clock alkene **123** under a) radical conditions and b) cationic conditions.<sup>272,273</sup>

Unfortunately, alkene **123** proved to be inert to the developed reaction conditions, making us unable to draw any useful conclusions from this experiment (Scheme 2.41).



**Scheme 2.41** Radical-clock alkene **123** was unreactive under the developed reaction conditions.

An alternative probe into the electronic nature of reactions is the use of stable- persistent radicals species, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) **124** or galvinoxyl free radical **125**, as additives. Persistent radical species can react with radical intermediates and act to inhibit radical reactions. Observation of diminished yields, or adducts between the substrate and the persistent radical additive provide evidence for radical intermediates in reactions.<sup>274,275</sup> However it should be noted that diminished catalytic reaction yields in the presence of free radical additives may simply be due to reactions between the additive and the metal catalyst.<sup>276,277</sup>

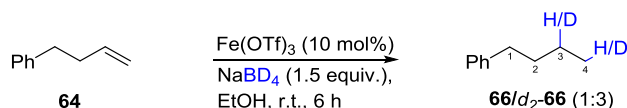


**Scheme 2.42** Use of persistent radicals as reaction inhibitors.

The formal hydrogenation of 4-phenyl-1-butene **64** was attempted in the presence of 10 mol% of either TEMPO or Galvinoxyl free radical additives. In both cases complete inhibition of the alkene hydrogenation was observed. No evidence of adducts of the alkene and free radicals species were observed.

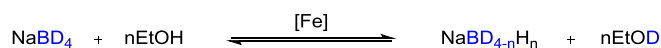
#### 2.4.4.2 Deuterium Labelling Reactions

In order to investigate both the mechanism of the reaction and the origin of the added hydrogen, deuterium incorporation experiments were carried out. Simply performing the formal hydrogenation of 4-phenyl-1-butene **64** with NaBD<sub>4</sub> resulted in a mixture of protio- and deuterio- products (Scheme 2.43), with the deuterium incorporated at both the C3 and C4 positions of the alkane.



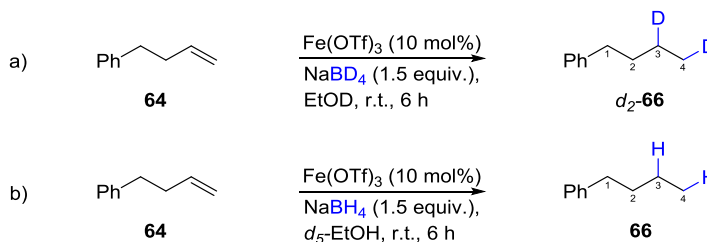
**Scheme 2.43** Initial deuterium labelling experiment, resulting in a mixture of deuterated products

This mixture of deuterated products may result from an ensemble of hydrogenation mechanisms/catalysts or an unselective hydrometallation step. However, assuming that a single mechanism is responsible for the formation of the hydrogenation products, it must be the case that scrambling of the deuterium label between the formal nucleophile and the formal electrophile must be occurring. Deuterium exchange between NaBD<sub>4</sub> and alcoholic solvents, under metal catalysed conditions has been previously reported (Scheme 2.44),<sup>278</sup> and this is proposed to be responsible for the mixture of deuteration products.



**Scheme 2.44** Proposed exchange of deuterium label between NaBD<sub>4</sub> and EtOH.<sup>278</sup>

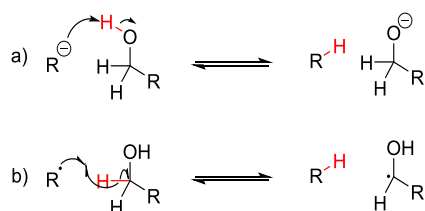
In order to mitigate the results of this deuterium scrambling, reactions were performed where the label was placed on both the exchangeable positions of the boron hydride and the acidic proton on ethanol. Reduction of 4-phenyl-1-butene **64** using NaBD<sub>4</sub> and *d*<sub>1</sub>-ethanol gave exclusively the dideuterated alkane *d*<sub>2</sub>-**66** (Scheme 2.45 a). When *d*<sub>5</sub>-EtOH was used as the reaction solvent, in the presence of NaBH<sub>4</sub>, no deuterium incorporation was observed (Scheme 2.45 b).



**Scheme 2.45** Revised deuterium labelling experiments, giving a) fully deuterated product *d*<sub>2</sub>-**66** and b) fully protonated product **66**.

Proton incorporation from ethanol could occur by two distinct mechanisms. Firstly an alkyl-anion intermediate can deprotonate ethanol at the alcoholic proton (Scheme 2.46 a). Alternatively, an alkyl-radical intermediate can abstract a proton from the alkyl-chain of ethanol (Scheme 2.46 b) to generate the most stable radical intermediate.

That no scrambling of the label is observed when both the exchangeable hydrogens are labelled (Scheme 2.45) strictly rules out the possibility of the formation of an alkyl-radical intermediate that can then abstract a proton from ethanol. These results unfortunately do not provide any data on whether both, or only one hydrogen is incorporated from NaBH<sub>4</sub>.

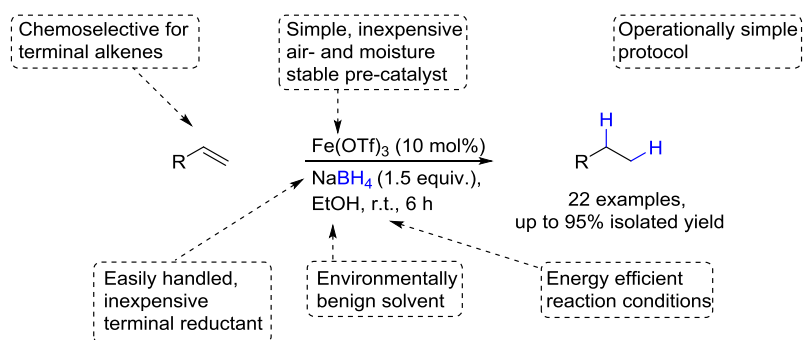


**Scheme 2.46** Mechanisms of proton incorporation from ethanol by a) an anionic intermediate and b) a radical intermediate.

Further mechanistic investigations were not performed due to time constraints of the project.

## 2.5 CONCLUSIONS

In summary an operationally simple and environmentally benign formal hydrogenation protocol has been developed using highly abundant iron(III) salts and an inexpensive, bench stable, stoichiometric reductant,  $\text{NaBH}_4$ , in the ‘green’ solvent ethanol, under ambient conditions. This reaction has been applied successfully to the reduction of a variety of terminal alkenes bearing numerous functional groups. Styrene derivatives have been shown to be hydrogenated under the developed reaction conditions, but competitive polymerisation reactions appear to limit the yields achievable with these substrates to around a maximum of 58%. A limited number of acrylate and acrylamide derivatives have also been successfully hydrogenated. Irrespective of the type of alkene used, dienes, internal alkenes, 1,1-disubstituted alkenes and 1,2-disubstituted alkenes all proved to be largely inert to the conditions developed, typically generating <10% hydrogenation products. Alkynes were extremely poor substrates for the hydrogenation reaction, requiring a large excess of  $\text{NaBH}_4$  to achieve even a poor hydrogenation yield (20 equivalents of  $\text{NaBH}_4$  gave only 34% **91**). Additionally the presence of alkynes suppressed the hydrogenation of alkenes in the same reaction mixture.



**Scheme 2.47** Summary of the alkene formal hydrogenation developed in this work

The initial mechanistic investigations into the nature of  $\text{Fe(OTf)}_3$  catalysed,  $\text{NaBH}_4$  mediated, formal hydrogenation reaction have been reasonably inconclusive. Radical inhibition experiments completely inhibited the reaction, suggesting that they irreversibly bind to the catalyst. Deuterium labelling studies indicate that this reaction proceeds by an ionic rather than

radical mechanism, but offer little information on either the identity of the catalytically active species or the mechanism of hydrogenation.

This work has been published in Organic and Biomolecular Catalysis (*Org. Biomol. Chem.* **2014**, *12*, 5082-5088, DOI: 10.1039/C4OB00945B, see Appendix 1).

Finally, during the hydrogenation of nitro group containing substrates, it was found that the nitro group was also hydrogenated, suggesting the possibility of re-optimising the reaction for nitro group hydrogenation. This work is reported in the following chapter.



# CHAPTER 3. OPERATIONALLY SIMPLE, FORMAL HYDROGENATION OF NITRO GROUPS USING $\text{Fe}(\text{OTf})_3$ AND $\text{NaBH}_4$

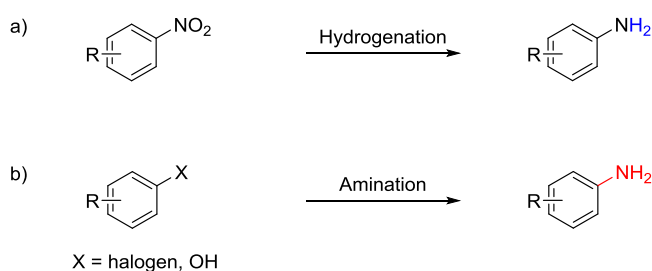
## 3.1 PREAMBLE

Chapter 3 consists of two major sections, the first of which is a background section comprising of: firstly a brief introduction to nitroarene hydrogenation chemistry; secondly a comprehensive review of recent developments in iron-catalysed nitro group hydrogenation reactions; thirdly a summary of the state-of-the-art in iron-catalysed formal hydrogenation reactions of nitro groups and how this project aims to add to the sum of knowledge on the subject. The second section consists of the author's research into developing a novel iron-catalysed formal hydrogenation of alkenes comprising of: development of the initial lead reactivity into optimised reaction conditions; and the substrate scope of the reaction. Much of the practical work on this project was performed by the following undergraduate students, acting under the author's direct supervision: Ming-Ming Tran, Jenifer E. Nelson and G. Usherwood Sloan.

## 3.2 INTRODUCTION

### 3.2.1 NITRO GROUP REDUCTION: GENERAL BACKGROUND

The synthesis of arylamines is an important target in organic synthesis, due to the wide utility of these compounds in the production of dyes, pigments, agrochemicals and pharmaceutical compounds.<sup>279</sup> Typical routes to aromatic amines involve either the hydrogenation of nitro groups or the amination of phenols and halo-arenes (Scheme 3.01).<sup>280</sup>

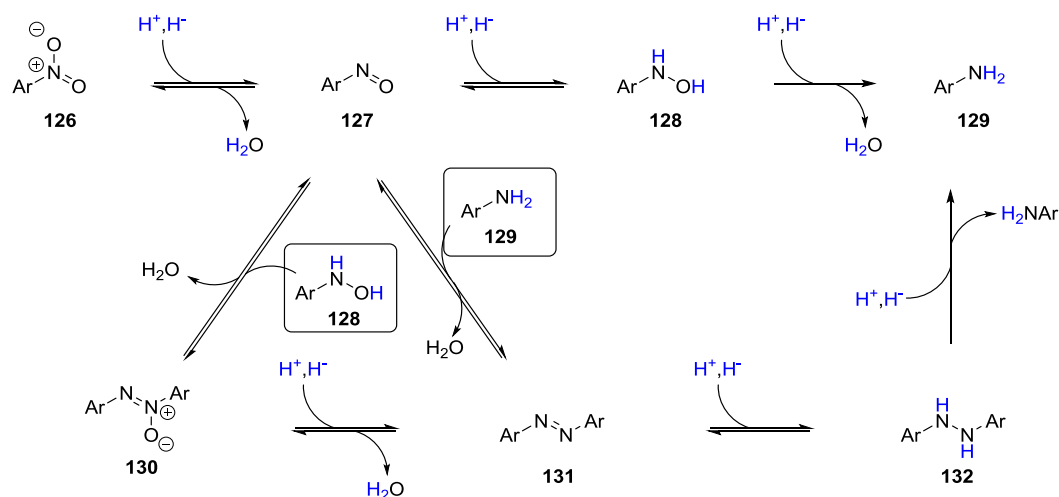


**Scheme 3.01** Typical routes to aryl-amines.<sup>280</sup>

Nitro groups are reduced to aniline derivatives in a 6-electron, 6-hydrogen reaction with the elimination of two equivalents of water that typically follows one of a number of interconnected pathways (Scheme 3.02).<sup>281,282</sup>



The direct pathway consists of sequential 2-electron reductions of the nitroarene **126** to the nitrosoarene **127**. This is then reduced to the *N*-aryl-hydroxylamine **128** and finally to the aryl-amine **129**. Alternatively, reaction intermediates can condense, typically the nitrosoarene **127** and the *N*-aryl-hydroxylamine **128** to form azoxyarenes **130**, and the resulting dimers are then reduced *via* the azoarene **131** and hydrazoarene **132**. It should be noted that other condensation reactions are possible, such as the aryl-amine product **129** and the nitrosoarene **127** to give the azoarene **131**. Additionally, since water is generated in this reaction, these condensation reactions are all reversible leading to a large number of possible intermediates present in any given reaction mixture. Predicting the thermodynamically favourable pathway for a given reagent under any given reaction conditions can be problematic. Additionally care needs to be taken during the development of new reaction methodologies since some of these intermediates, particularly the hydroxylamine **128** and azoarene **131**, are known carcinogens and are capable of undergoing violent disproportionation reactions. Preventing the accumulation of these potentially explosive intermediates is crucial to the development of safe and environmentally benign reactions.



**Scheme 3.02** General scheme for nitroarene reduction.<sup>281,282</sup>

The first reported reduction of nitro groups to amines was by Béchamp in 1854, using stoichiometric iron powder and hydrochloric acid.<sup>283</sup> Since then a huge range of techniques have been developed including: the use of powerful stoichiometric hydride sources, such as  $\text{LiAlH}_4$ ;<sup>284</sup> and wide variety of catalytic reductions.<sup>11</sup> Particularly prevalent is the use of heterogeneous and nanoparticulate palladium, platinum, and nickel pre-catalysts.<sup>285</sup>

Of significant concern during the development of catalytic methods of nitro group reduction is the chemoselectivity of the reaction.<sup>282</sup> Typical functional groups that can be vulnerable to catalytic reductive conditions include: halogen substituents, alkenes, nitriles, heterocycles and carbonyl derivatives. While many traditional methods are appropriate for the reduction of

simple unfunctionalised nitroarenes, highly substituted nitrocompounds require better tuned catalytic reductions. This has led to both empirical tuning of existing systems by the use of various additives and catalyst poisons,<sup>286</sup> and also to the development of novel homogeneous catalytic systems with well-defined selectivities.

In line with the general trend in modern chemistry towards the development of more environmentally benign catalytic systems, iron-catalysed nitro group reduction has been a field of considerable development in recent years. The current state-of-the-art in iron-catalysed nitro group hydrogenations, transfer hydrogenations and formal hydrogenations is discussed below.

### 3.2.2 RECENT DEVELOPMENTS IN IRON-CATALYSED NITRO GROUP REDUCTIONS

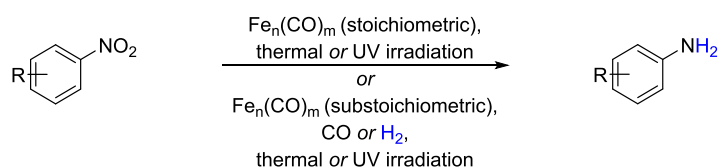
#### 3.2.2.1 Iron-Carbonyl Species as Hydrogenation Catalysts

First reported in 1925,  $\text{Fe}_3(\text{CO})_{12}$  is able to act as a stoichiometric reductant to reduce nitrobenzene to aniline and reductively coupled azo-derivatives.<sup>287</sup> A range of starting iron-carbonyl complexes were later utilised:  $[\text{HFe}(\text{CO})_4]^-$ ,<sup>288–290</sup>  $\text{Fe}(\text{CO})_5$ ,<sup>287,290–297</sup>  $\text{Fe}_3(\text{CO})_{12}$ ,<sup>291,298–303</sup> or  $[\text{HFe}_3(\text{CO})_{11}]^-$ .<sup>304,305</sup> The conditions of these reductions vary widely in different reports: some examples use strong aqueous bases under biphasic conditions; others use polymer or alumina supports; fluoride sources; or act under high temperatures and  $\text{H}_2$  pressures.

A considerable amount of debate has gone into determining the mechanism by which these complexes act on nitro groups. Some examples report at least one equivalent of  $\text{CO}_2$  being generated from these reductions, indicating that at least one of the oxygen atoms from the nitro group is being lost following addition to CO.<sup>295,303</sup> Hypothesising that the loss of CO ligands may be responsible for the consumption of the iron-carbonyl reductant, Cole *et al.* were able to make this reaction catalytic by performing it under high temperatures and CO (115 atm).<sup>290</sup> Other catalytic examples used highly pressurised atmospheres of  $\text{H}_2$ .<sup>293,294</sup>

Under basic conditions it is known that  $\text{Fe}_3(\text{CO})_{12}$  and  $\text{Fe}(\text{CO})_5$  are activated to salts of  $[\text{HFe}_3(\text{CO})_{11}]^-$  and  $[\text{HFe}(\text{CO})_4]^-$  respectively.<sup>288</sup> Salts of both these ions were also successfully used as reductants and for many years it was presumed that these species acted as hydride donors. The mechanistic investigations have been hindered by the ease of interconversion between iron-carbonyl species, and the spectroscopic similarities of many of the intermediates. More recent reports indicate that rather than a single active species, a number of iron-carbonyl species generated *in situ* act in concert. In the case of  $\text{Fe}_3(\text{CO})_{12}$  the corresponding hydride species  $[\text{HFe}_3(\text{CO})_{11}]^-$  was shown not to be reductively active. Additionally the radical anion  $[\text{Fe}_3(\text{CO})_{11}]^{\cdot -}$  has been isolated as a salt with both  $\text{PPh}_4^+$  and  $(\text{PPh}_3)_2\text{N}^+$  counterions and characterised by X-ray crystallography, EPR and IR, and been shown to be generated under the

reaction conditions.<sup>306,307</sup> The initial reaction with the nitroarene is thought to be performed by the radical cluster  $[\text{Fe}_3(\text{CO})_{11}]^-$ , with the *in situ* generated  $[\text{HFe}(\text{CO})_4]^-$  probably responsible for a second reduction step.<sup>308</sup>  $[\text{HFe}(\text{CO})_4]^-$  appears to be the main reductively active species when  $\text{Fe}(\text{CO})_5$  is used as the starting iron(0) carbonyl species.

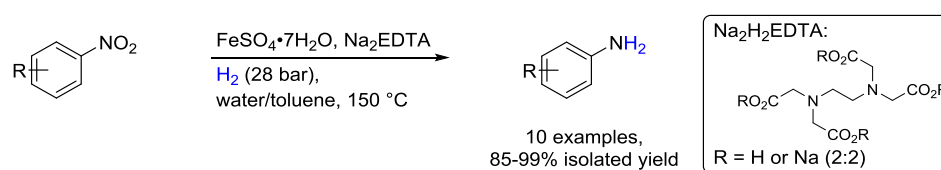


**Scheme 3.03** Nitroarene reduction, mediated by iron(0) carbonyl species species under either stoichiometric or substoichiometric conditions.<sup>288–305</sup>

It should be noted that all the previously discussed drawbacks of iron(0) carbonyl chemistry, namely the acute toxicity, volatility and flammability of the complexes also applies to this work. These reactions have limited ‘green’ chemistry credentials and will not be discussed in greater detail.

### 3.2.2.2 Iron-Catalysed Nitro Group Hydrogenation Reactions

Chaudhari and co-workers reported a biphasic system using a water-soluble iron catalyst to hydrogenate nitrobenzene derivatives (10 examples, 84.6–99.0% isolated yield, Scheme 3.04) at 150 °C and  $\text{H}_2$  (28 atm).<sup>309</sup> The use of ethylenediaminetetraacetate (EDTA) as a ligand for  $\text{FeSO}_4$  solubilised the iron complex in the aqueous phase (less than 5 ppm in the organic phase); in the absence of ligand up to 80 % of the iron salt was leached into the organic phase. The aqueous phase was successfully recycled 5 times with a fresh organic phase with no loss of activity, to give a cumulative turn over number (TON) of 6665. Carboxylic acid, ketone, ether, amine and nitrile substituents were all well tolerated by the system, and chloronitrobenzenes were not dehalogenated. Azoxybenzene, azobenzene and also hydroxylamine intermediates were detected.

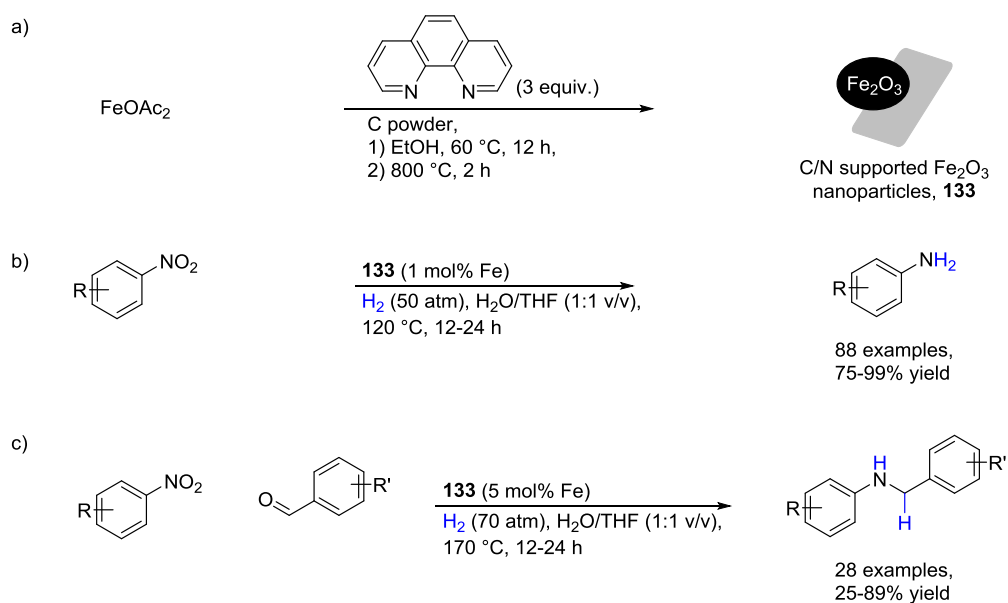


**Scheme 3.04** Hydrogenation of nitroarenes reported by Chaudhari and co-workers under thermal conditions.<sup>309</sup>

The group of Beller has produced a range of immobilised iron(II) oxide nanoparticles by mixing iron(II) acetate, phenanthroline (3 equivalents) and a solid support in ethanol, then pyrolysing the resulting mixture.<sup>310</sup> These materials were characterised by TEM, X-ray photoelectron

spectroscopy (XPS), electron paramagnetic resonance (EPR) spectroscopy, and Mössbauer spectroscopy. The material produced using carbon-powder support, pyrolysed at 800 °C **133** (Scheme 3.05 a) was characterised as iron(II) oxide particles (3%wt) of two different size ranges, larger particles of 20-80 nm and smaller particles of 2 to 5 nm diameter. The iron(II) oxide nanoparticles were surrounded by layers of nitrogen doped graphene, and the iron particles appeared to be coordinated by *N*-ligands. The supported iron oxide species **133** (1 mol% Fe) were demonstrated to be an effective pre-catalyst for the hydrogenation, under H<sub>2</sub> (50 atm) and thermal activation (120 °C), of nitroarenes (88 examples, 75-99% yield, Scheme 3.05 b). While these reaction conditions require considerable energy input, the hydrogenation reaction proved to have excellent chemoselectivity for nitro groups. The substrate scope includes complex drug-like molecules and examples of substrates containing reducible functionalities including alkenes, alkynes, boronic esters, nitriles, amides, esters, ketones and aldehydes.

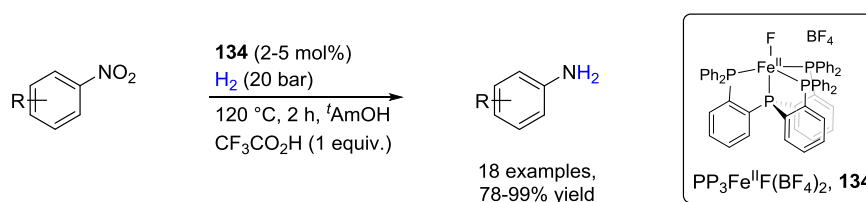
The supported nanoparticles **133** have also been reported for the reductive amination of nitro compounds (28 examples, 25-89% yield, Scheme 3.05 c), albeit under even more forcing conditions of H<sub>2</sub> (70 atm) and 170 °C.<sup>311</sup>



**Scheme 3.05** a) Production of C/N supported Fe<sub>2</sub>O<sub>3</sub> nanoparticles **133** and the use of **133** for b) the hydrogenation of nitroarenes,<sup>310</sup> and c) the reductive amination of nitro compounds.<sup>311</sup>

The group of Beller has also developed numerous systems for nitroarene reduction using iron complexes supported by multidentate phosphine ligands. It was found that under H<sub>2</sub> (20 atm) at 120 °C, in the presence of 1 equivalent of trifluoroacetic acid (TFA), complex **134** supported by a thermally-stable tetradentate phosphine ligand was active for the hydrogenation of a range of

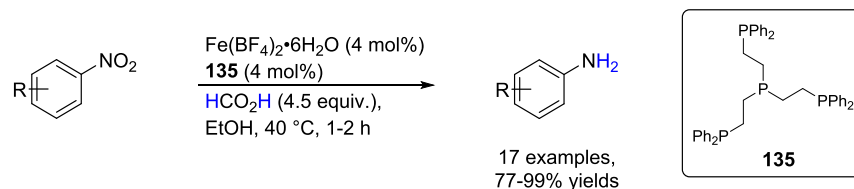
nitroarenes (18 examples, 78-99% yield, Scheme 3.06).<sup>312</sup> The well-defined complex and the one formed *in situ* were equally active.



**Scheme 3.06** Hydrogenation of nitroarenes by phosphine supported complex **134**, reported by Beller.<sup>312</sup>

### 3.2.2.3 Iron-Catalysed Transfer Hydrogenations of Nitro Groups

Beller and co-workers have reported the use of formic acid as the terminal reductant for the transfer hydrogenation of nitroarenes (17 examples, 77-99% yield), catalysed by iron(II) tetrafluoroborate in conjunction with tetradentate phosphine ligand **135** in ethanol at 40 °C (Scheme 3.07).<sup>313</sup> This reaction was not active under of H<sub>2</sub> (5 atm), suggesting that the reaction did not proceed by hydrogen evolved from the formic acid, but rather by transfer hydrogenation. Interestingly for a transfer hydrogenation, no additional base was required. This system was highly active for the reduction of nitroarenes and left alkenes, ketones and esters intact. Catalytic intermediates existed as <1% of the reaction mixture, and the direct reduction pathway appeared to be the dominant system.

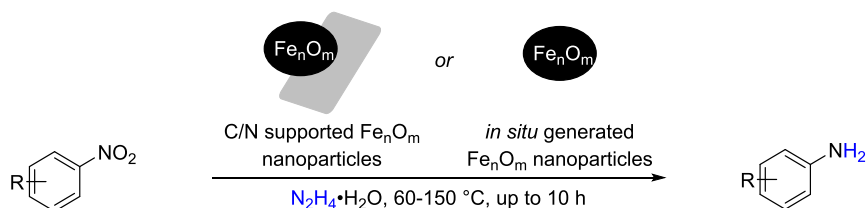


**Scheme 3.07** Transfer hydrogenation of nitroarenes reported by Beller and co-workers.<sup>313</sup>

A number of iron-catalysed transfer hydrogenation protocols have been developed using the toxic and carcinogenic terminal reductant: hydrazine hydrate.

The group of Singh has reported 3 different catalytic systems for nitroarene hydrogenation using hydrazine hydrate at 120 °C in a mixture of H<sub>2</sub>O and EtOH (1:1 v/v): firstly using FeSO<sub>4</sub>·7H<sub>2</sub>O, secondly using iron(II) phthalocyanine and thirdly using a mixture of the two (19 examples, up to 99% yield).<sup>314</sup> The group of Bhanage has reported the synthesis of iron-containing ionic liquids immobilised on to silica supports which are active, recyclable catalysts for the transfer hydrogenation of nitroarenes in ethylene glycol, at 110 °C using hydrazine hydrate as the terminal reductant (33 examples, 72-99% conversion).<sup>315</sup>

Several groups have developed iron oxide nanoparticles as pre-catalysts for this reaction, in some cases immobilised on to solid supports (Scheme 3.08). The group of Beller has generated iron oxide particles supported on nitrogen doped graphene, prepared a similar manner to **133** (*vide supra*) and used these as catalysts for the transfer hydrogenation of nitroarenes with hydrazine hydrate at 100 °C in THF (48 examples, 90-99% yield).<sup>316</sup> The group of Kiwi-Minsker has developed Fe<sub>2</sub>O<sub>3</sub> nanoparticles (~2 nm diameter) immobilised on to activated carbon fibres (ACF), which at 2 mol% loading are highly active for nitroarene reduction with hydrazine hydrate (3 equiv.) in EtOH under the relatively mild conditions of 60 °C for up to 7 h (10 examples, all >95% yield).<sup>317</sup> The group of Kappe has developed a system using Fe(acac)<sub>3</sub> (0.25 mol%) and hydrazine hydrate (1.8 equiv.) in MeOH at 150 °C under microwave conditions.<sup>318</sup> Identical results were observed with several iron(II/III) pre-catalysts, High resolution TEM revealed that crystalline Fe<sub>3</sub>O<sub>4</sub> nanoparticles of 6 ± 2 nm diameter were formed *in situ* under the reaction conditions, these particles could be recycled without loss of catalytic activity. The system was exploited for the hydrogenation of nitroarenes (20 examples, 95-99% yield), nitroalkanes (4 examples, 96-99% yield) and azoarenes (5 examples, 97-99% yield) and modified for use in a continuous flow system.<sup>319</sup>



**Scheme 3.08** Several groups have reported the use of iron oxide nanoparticles, either with C/N supports or generated *in situ*, for the transfer hydrogenation with aqueous N<sub>2</sub>H<sub>4</sub> of nitroarenes.<sup>316–319</sup>

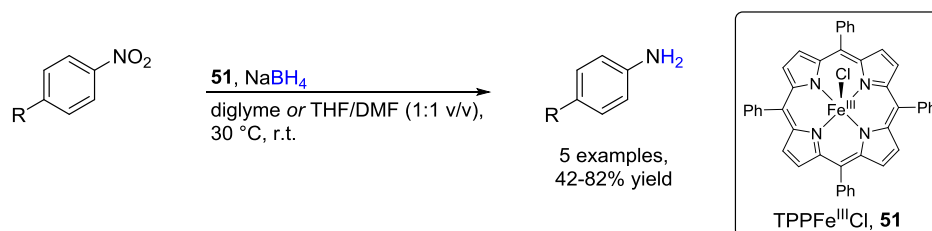
The considerably less hazardous terminal reductant *t*PrOH has been used in iron-catalysed transfer hydrogenations, however this typically requires a stoichiometric base and to the best of the author's knowledge has only been performed with heterogeneous iron oxide pre-catalysts.<sup>320,321</sup>

#### 3.2.2.4 Iron-Catalysed Formal Hydrogenations of Nitro Groups

Sakaki *et al.* used several metalloporphyrins as models for the active site of the nitrite reductase enzyme.<sup>322,323</sup> NaBH<sub>4</sub> was used as a model hydride source in place of the biological reductant nicotinamide adenine dinucleotide phosphate hydride (NADPH). Of the three metalloporphyrins used, Fe<sup>III</sup>(I<sup>+</sup>TP)Cl **51** was the most active and able to catalyse the reduction of nitrobenzene derivatives to the corresponding arylamine (Scheme 3.09).

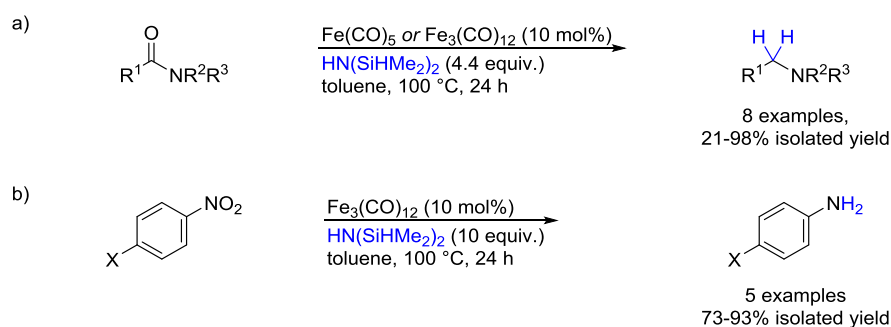
UV-vis spectroscopy and EPR measurement showed that NaBH<sub>4</sub> was able to reduce [Fe<sup>III</sup>(I<sup>+</sup>TP)]<sup>+</sup> to [Fe<sup>I</sup>(I<sup>+</sup>TP)]<sup>-</sup>, but in the presence of nitrobenzene derivatives, only Fe<sup>II</sup> species

were present; these were presumed to be catalytically active. The initial investigation used only diglyme as the solvent. Reactions were unsuccessful in both THF and DMF: NaBH<sub>4</sub> is very poorly soluble in THF and DMF was found to coordinate the metalloporphyrin too strongly. A mixture of THF and DMF (1:1 v/v) on the other hand was found to be as active as diglyme. Addition of MeOH to the diglyme significantly increased the rate of reaction; this was proposed to be due to protonation events favouring the one-electron reduction of nitrobenzene. Electron-withdrawing substituents on the nitrobenzene derivatives favoured the reduction, whereas electron-donating substituents disfavoured it (5 examples, 42-82%).



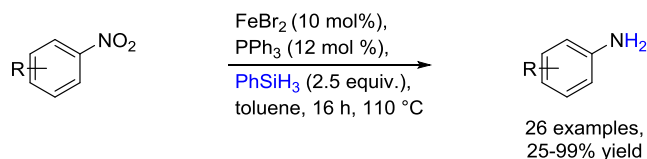
**Scheme 3.09** TPPFe<sup>III</sup>Cl **51** catalysed hydrogenation of nitrobenzene derivatives, reported by Sakaki *et al.*<sup>322,323</sup>

Nagashima and co-workers reported intriguing chemoselectivity in the first iron-catalysed hydrosilylation of a nitroarene by an Fe<sub>3</sub>(CO)<sub>12</sub> and 1,1,3,3-tetramethyldisilazine.<sup>324</sup> When activated by thermal or UV irradiation, the iron-catalysed reduction of amides to amines in the presence of silanes was performed (Scheme 3.10 a). However when *N,N*-dimethyl-*p*-nitrobenzamide was subjected to thermal reductive conditions with a large excess of HN(SiHMe<sub>2</sub>)<sub>2</sub>, *N,N*-dimethyl-*p*-aminobenzamide was recovered as the only product in 77% isolated yield. This reactivity was not observed under similar conditions using noble metal catalysts. The nitro reduction occurred faster than the amide reduction, and the amines formed *in situ* acted as a functional-group-selective poison for the catalyst. Methoxy- and halide substituted nitroarenes (5 examples, 73-93%, Scheme 3.10 b) were successfully reduced to the corresponding amine and no proto-dehalogenation was observed.



**Scheme 3.10** Reduction by hydrosilylation of a) amides and b) nitroarenes, catalysed by iron(0) carbonyl complexes.<sup>324</sup>

The reduction of nitroarenes by hydrosilylation was also investigated by Beller and co-workers,<sup>325</sup> and following a screen of iron salts in the presence of PCy<sub>3</sub>, FeBr<sub>2</sub> and FeI<sub>2</sub> were identified as highly active catalysts. Further optimisation with FeBr<sub>2</sub> revealed that monodentate phosphine ligands with either aromatic or bulky groups resulted in a highly reactive species. The use of chelating phosphines resulted in considerably diminished yields, as did the use of aryl and alkyl silanes bearing only one Si-H group. PhSiH<sub>3</sub>, in conjunction with FeBr<sub>2</sub> and PPh<sub>3</sub>, was used to perform the hydrosilylation of a range of nitroarenes, resulting in the reduction to aniline derivatives (25 examples, 25-99% yield, Scheme 3.11). No protodehalogenation of -Cl, -Br or -F substituents, irrespective of ring position, was reported and readily reduced functionality including cyano, alkene and ester groups were all tolerated.

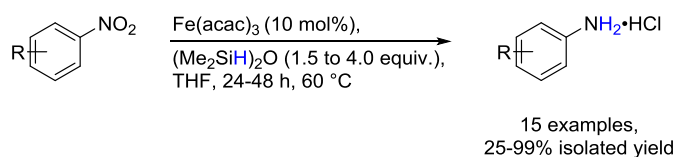


**Scheme 3.11** Reduction by hydrosilylation of nitroarenes, catalysed by FeBr<sub>2</sub> and PPh<sub>3</sub>.<sup>325</sup>

A similar reduction by hydrosilylation under more mild, ligand free conditions was reported very shortly afterwards by Lemaire and co-workers.<sup>326,327</sup> Both Fe(acac)<sub>2</sub> and Fe(acac)<sub>3</sub>, were active for the reduction of nitroarenes with (Me<sub>2</sub>SiH)<sub>2</sub>O as the stoichiometric reductant. The Fe<sup>III</sup> salt was used for substrate screening due to its lower cost. Likewise the less expensive solvent THF was used for screening although the more environmentally benign 2-MeTHF was also used successfully. The reduction of a number of nitrobenzene derivatives was demonstrated (15 examples, 25-99% isolated yield, Scheme 3.12), including nitroarenes with bromide substituents which were successfully reduced with no protodehalogenation. Additionally nitro groups were successfully reduced in the presence of carboxylic acids, nitriles and esters, although esters did require more forcing conditions (48 h, 90 °C in toluene). However the reaction was not selective

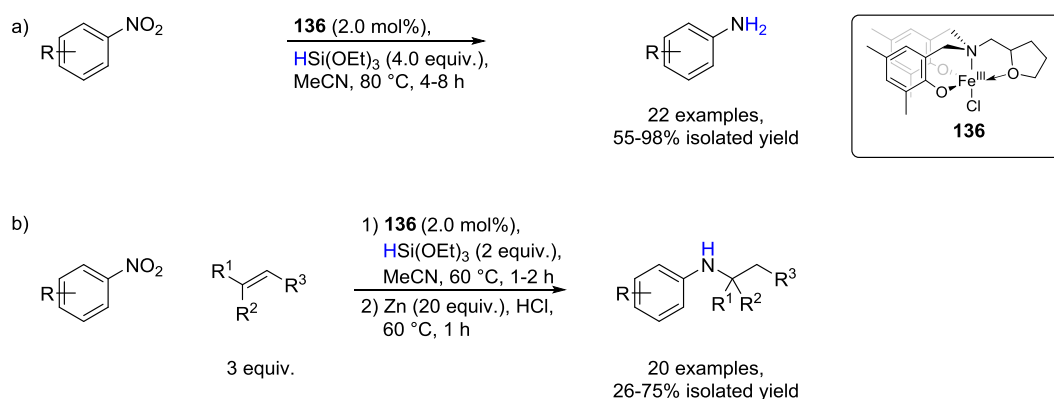


for the reduction of nitro groups in the presence of aldehydes, and when substrates bearing both functional groups were used, both functional groups were reduced.



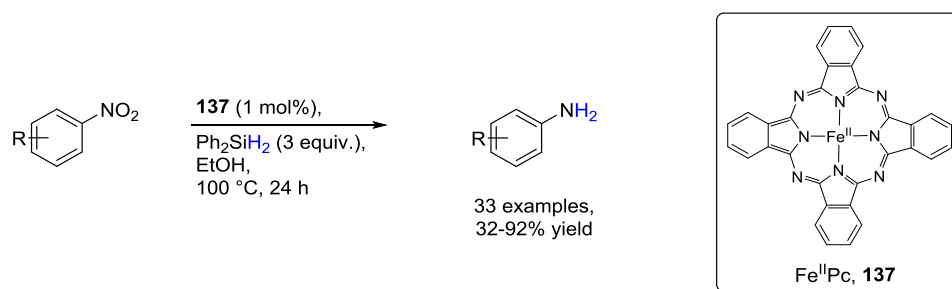
**Scheme 3.12** Reduction by hydrosilylation of nitroarenes, catalysed by  $\text{Fe}(\text{acac})_3$ .<sup>326,327</sup>

The groups of Shaver and Thomas have reported the formal hydrogenation of nitroarenes using amine-bis(phenolate) iron(III) complex **136** (2 mol%),  $\text{HSi}(\text{OEt})_3$  (4 equiv.) in MeCN at 80 °C (22 examples, 55-96% isolated yield, Scheme 3.13 a).<sup>328</sup> This system was also exploited for the hydroamination of alkenes (20 examples, 26-75% isolated yield, Scheme 3.13 b).<sup>329</sup> The system demonstrated good chemoselectivity and could be applied to ligand precursors and drug-like molecules.



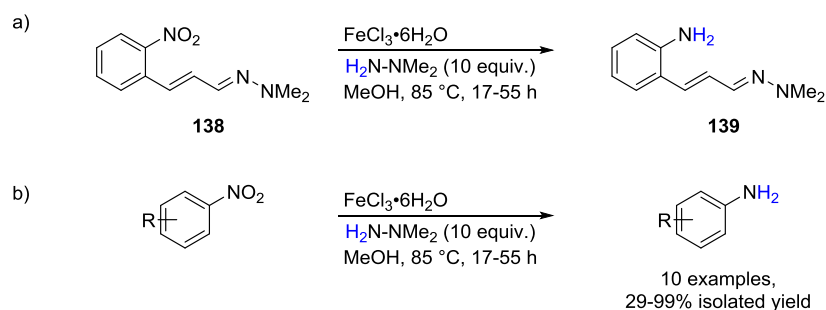
**Scheme 3.13** Shaver and Thomas' a) formal hydrogenation of nitroarenes and b) application to formal hydroamination of alkenes.<sup>328,329</sup>

The group of Singh screened a large number of metal(II) phthalocyanine species along with various stoichiometric reductants for the reduction of nitroarenes.<sup>330</sup> Two distinct systems were developed: firstly iron(II) phthalocyanine **137**, in the presence of  $\text{Ph}_2\text{SiH}_2$  was used (33 examples, 32-92% yield, Scheme 3.14); secondly palladium(II) phthalocyanine was used in conjunction with  $\text{NaBH}_4$  (18 examples, 50-99% yield).



**Scheme 3.14** Reduction by hydrosilylation of nitroarenes, catalysed by iron(II) phthalocyanine **137**.<sup>330</sup>

While attempting to develop a transfer hydrogenation of compound **138** to aniline **139** using hydrazine, Kerr and co-workers stumbled upon the use of 1,1-dimethylhydrazine in the presence of  $\text{FeCl}_3$  (Scheme 3.15 a).<sup>331</sup> Transfer hydrogenation reactions using hydrazine as a stoichiometric reductant typically proceed by elimination of  $\text{H}_2$  across the N-N bond, however not only is this not possible for 1,1-dimethylhydrazine but hydrazine itself was completely unreactive, strongly implying that this is not the mechanism responsible for the process. Examples of nitroarenes were successfully reduced using this protocol (10 examples, 29-99% isolated yield, Scheme 3.15 b). Interestingly treatment of nitrocinnamaldehyde under these conditions also resulted in aniline **139**. Since the aldehyde can be recovered by hydrolysis of the hydrazone, this represents a route to a chemoselective reduction of an aromatic nitro group in the presence of carbonyl derivatives. This method was unsuccessful for the reduction of aliphatic nitro compounds such as 2-phenylnitroethane.



**Scheme 3.15** Reduction of nitroarenes by the group of Kerr.<sup>331</sup>

Iron oxide species have been reported as supports for numerous other metal catalysts.<sup>332</sup> The group of Thakore has reported that mixed phase iron oxide ( $\text{Fe}_2\text{O}_3$  and  $\text{Fe}_3\text{O}_4$ ) nanoparticles can be active catalysts for the formal hydrogenation of *p*-nitroaniline with  $\text{NaBH}_4$  (5.1 equiv.) in water, however only poor yields (*ca.* 55%) were obtained.<sup>333</sup> The catalytic activity of the system could be improved when the iron oxide nanoparticles were used to template the growth of crystalline  $\text{Ni}^0$  species. The resulting mixed  $\text{Fe}_n\text{O}_m/\text{Ni}^0$  nanoparticles were highly active species for the formal hydrogenation of nitroarenes (27 examples, 89-95% isolated yield) using  $\text{NaBH}_4$  (4 equiv.) in water, at room temperature with short reaction times (<50 min). Additionally, the

group of Sharma has reported that  $\text{Fe}_3\text{O}_4$  nanoparticles that are poor catalysts (12% conversion) for the reduction of *o*-nitroaniline with  $\text{NaBH}_4$  (loading not reported) in water.<sup>334</sup> The  $\text{Fe}_3\text{O}_4$  nanoparticles were encapsulated with silica, functionalised with tethered amine groups and then treated with  $\text{Cu}(\text{acac})_2$ . The resulting species were considerably more active, in the presence of  $\text{NaBH}_4$ , for the formal hydrogenation of nitroarenes (12 examples, 90-100% conversion).

### 3.3 PROJECT AIMS

Precious metal-catalysed nitro group hydrogenation reactions are well established and extremely common in both industrial and academic settings. The use of  $\text{Pd/C}$  and  $\text{H}_2$  is ubiquitous in nitro group reduction reactions, however the use of such systems typically raises safety concerns regarding a pyrophoric catalyst and pressurised, flammable terminal reductant. Additionally, with such a promiscuous catalyst, the chemoselectivity of such a system requires empirical tuning of catalyst selectivity on a per-substrate basis.

As previously established, the development of more sustainable chemical systems is of critical importance. Many effective systems for iron-catalysed nitro group hydrogenation have been reported including examples with good chemoselectivity. However, most of these systems require: lengthy catalyst syntheses; high temperatures; prolonged reaction times; and where applicable, high  $\text{H}_2$  pressures. For any iron-catalysed hydrogenation reaction to attain widespread use, it must have: a simple and available pre-catalyst; an easy to handle stoichiometric reductant; and environmentally benign reaction conditions. To date, very few iron-catalysed nitro group reductions have achieved these prerequisites.

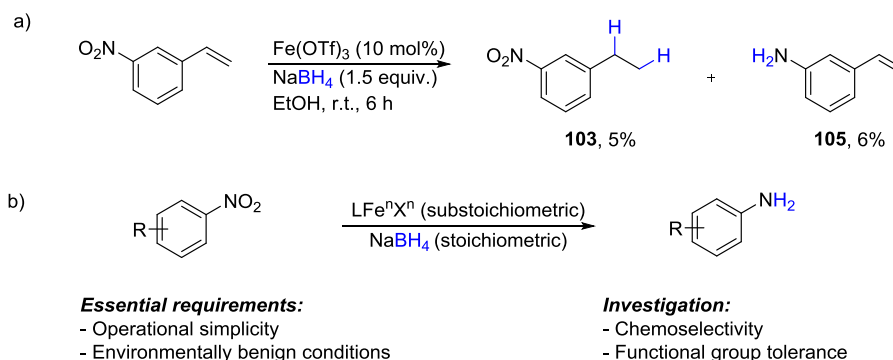
This project was conceived to develop an iron-catalysed nitro group reduction that addresses these requirements.  $\text{NaBH}_4$  was proposed as the preferred stoichiometric reductant, for the reasons discussed above (See Section 2.3).

When this work was performed, the only existing iron-catalysed nitroarene formal hydrogenation protocols using  $\text{NaBH}_4$  as the terminal reductant was the work of Sakaki and co-workers,<sup>322</sup> along with the iron oxide supported systems of Thakore and Sharma.<sup>333,334</sup> These systems are also unusual, for iron-catalysed nitro group reductions, in that they proceed at room temperature, without a requirement for an additional activating reagent. In the work of Sakaki, the reaction does however require the use of a high molecular weight iron-porphyrin catalyst, and has only undergone limited development.

During the previously discussed development of an alkene formal hydrogenation protocol using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ , 3-nitrostyrene was found to give a mixture of reaction products

corresponding competitive reduction of either the nitro group **93** or the alkene substituent **94** (Scheme 3.16 a).

Studies were instigated in order to optimise this unforeseen side-reaction into a viable nitro group hydrogenation. Ideally this iron-catalysed formal hydrogenation would be developed to be: broadly applicable with a good substrate scope; preferably tolerant of a wide range of functional groups; operationally simple; and environmentally benign (Scheme 3.16 b).



**Scheme 3.16** a) Initial lead reactivity was provided by the mixture of reduction products obtained from the hydrogenation of 3-nitrostyrene and b) general aims of this project.

## 3.4 RESULTS AND DISCUSSION

### 3.4.1 CATALYST IDENTIFICATION AND METHODOLOGY DEVELOPMENT

Using nitrobenzene **140** as a model substrate, simple iron salts were investigated for catalytic activity in the reduction of the nitro group to primary amines. EtOH was used as the preferred solvent again due to its environmentally benign nature, and the good solubility of iron salts and NaBH<sub>4</sub> in it.

FeCl<sub>3</sub> offers an inexpensive and readily available iron(III) source, however only limited conversion of nitrobenzene **140** to aniline **141** was observed when the reaction mixtures were stirred reacted in the presence of 2 equivalents of NaBH<sub>4</sub> (Table 3.4-1, Entry 1). Increasing the loading of NaBH<sub>4</sub>, first to 4 equivalents, then to 20, led to increased conversion of 51% and 88% respectively (Entries 2 and 3). The use of high-purity FeCl<sub>3</sub> ( $\geq 99.99\%$ ) again did not significantly change the observed reactivity (Entry 4).

Iron(II) salts FeCl<sub>2</sub> and Fe(OTf)<sub>2</sub> were less active than FeCl<sub>3</sub> for this formal hydrogenation of nitrobenzene (Entries 5 and 6).

However, use of Fe(OTf)<sub>3</sub> gave complete conversion to aniline (Entry 7), and allowed reaction times to be reduced to from 16 h to 4 h (Entry 9). Even using the apparently more active salt,

Fe(OTf)<sub>3</sub>, it was found that the quantity of NaBH<sub>4</sub> could not be reduced without diminishing conversion to the product (Entry 8).

**Table 3.4-1 Screening of iron(III) salts with NaBH<sub>4</sub> for the formal hydrogenation of nitrobenzene.<sup>a</sup>**

140  141

Entry	FeX <sub>2/3</sub>	NaBH <sub>4</sub> equiv.	t (h)	Conversion (%) <sup>b</sup>
1	FeCl <sub>3</sub>	2	16	15
2	FeCl <sub>3</sub>	4	16	51
3	FeCl <sub>3</sub>	20	16	88
4	FeCl <sub>3</sub> (99.99%)	20	16	90
5	FeCl <sub>2</sub>	20	16	62
6	Fe(OTf) <sub>2</sub>	20	16	60
7	Fe(OTf) <sub>3</sub>	20	16	99
8	Fe(OTf) <sub>3</sub>	10	16	32
9	Fe(OTf) <sub>3</sub>	20	4	99
10	BF <sub>3</sub> ·Et <sub>2</sub> O	20	4	0
11	AlCl <sub>3</sub>	20	4	0
12	HOTf	20	4	1

<sup>a</sup>Conditions: nitrobenzene (0.50 mmol), iron salt (10 mol%), NaBH<sub>4</sub> (equiv.), EtOH (4 ml, 0.13 M), r.t.. <sup>b</sup>Conversion measured by <sup>1</sup>H NMR spectroscopy.

Unfortunately, the large quantities of NaBH<sub>4</sub> required, often resulted in heterogeneous reaction mixtures, confounding attempts to perform effective reaction monitoring by <sup>1</sup>H NMR spectroscopy.

Control reactions were performed in the absence of an iron salt. Lewis acids: BF<sub>3</sub> and AlCl<sub>3</sub>, were ineffective as catalysts (Entries 10 and 11). Additionally, the use of a Brønsted acid (triflic acid, Entry 12) also resulted in only starting material being recovered. These results, along with the use of high purity FeCl<sub>3</sub> strongly suggest that species derived from the iron(III) pre-catalyst is the active catalytic species.

### 3.4.2 SUBSTRATE SCOPE

Using the optimised conditions of: Fe(OTf)<sub>3</sub> (10 mol%); NaBH<sub>4</sub> (20 equiv.); in EtOH; at room temperature; for 4 h, functional group tolerance of the formal hydrogenation of nitrobenzene derivatives was investigated (Table 3.4-2). Firstly, alkyl substituted nitrobenzene derivatives such as 2-, 3- and 4-methyl nitrobenzene and even the sterically hindered 2,6-dimethyl nitrobenzene were all successfully reduced to give the corresponding aniline derivatives in 49-80% isolated yield (**142-145**).

Methoxy- substituents were tolerated in the 2-, 3-, and 4- position around the arene ring, giving the amine products **146-148**. Additionally, 4-(methylthio)-aniline **149** was successfully produced

from the corresponding nitroarene in good yield. An example of a substrate bearing a free primary amine was reduced to give **150** in an acceptable yield of 44%. The same product could be obtained from 1,3-dinitrobenzene, albeit in only 6% yield. Nitro groups were successfully reduced in the presence of aryl- fluoride and chloride substituents without protodehalogenation to give the corresponding amines (**151-154**). 4-Bromonitrobenzene was, however, reduced to a mixture of both 4-bromoaniline **155** and the protodehalogenated product, aniline **141** (9%).

Nitroarenes bearing the electron-withdrawing trifluoromethyl- group were well tolerated by the formal hydrogenation protocol to give products **156** and **157** in 82% and 83% yields (by  $^1\text{H}$  NMR spectroscopy) respectively.

The chemoselectivity of the nitro group reduction in the presence of reducible functional groups was also investigated. Perhaps unsurprisingly, a substrate bearing a ketone substituent showed poor chemoselectivity with the carbonyl being reduced, by the background reactivity of  $\text{NaBH}_4$ , in addition to the nitro group (**158**). Interestingly, while this background reaction was also observed in the formal hydrogenation of alkenes previously developed (see section 2.4.3), in this case the desired nitro group reduction was not suppressed.

Ester and amide groups were tolerated without reduction under the reaction conditions, to give aniline derivatives **159-161** in 80-93% yield. These examples include the production of the analgesic benzocaine **160** in 93% yield (by  $^1\text{H}$  NMR spectroscopy). A methylsulfonyl substituted nitroarene was also successfully reduced to aminoarene **162**, albeit with an isolated yield of 53%. 4-Cyanonitrobenzene was successfully reduced to **163** without reduction of the nitrile functionality.

Disappointingly, an alkynyl substituted nitroarene **164** gave only an intractable mixture of reduction products. This is in keeping with the results observed above, whereby alkynes suppressed the formal hydrogenation of alkenes.

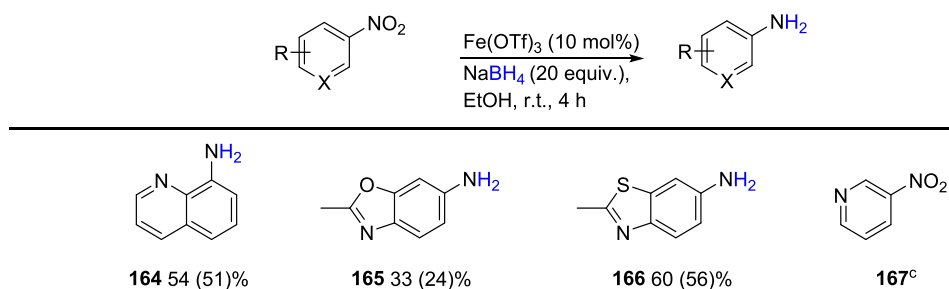
**Table 3.4-2 Formal hydrogenation of nitrobenzene derivatives using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ <sup>a,b</sup>**

$\text{R-C}_6\text{H}_4\text{NO}_2 \xrightarrow[\text{EtOH, r.t., 4 h}]{\text{Fe}(\text{OTf})_3 (10 \text{ mol}\%), \text{NaBH}_4 (20 \text{ equiv.})} \text{R-C}_6\text{H}_4\text{NH}_2$				
<b>141</b> 90 (80)%	<b>142</b> 80 <sup>c</sup> (80)%	<b>143</b> 61 <sup>c</sup> (49)%	<b>144</b> 73 (66)%	<b>145</b> 79 (59) <sup>d,e</sup>
<b>146</b> 76 <sup>c</sup> (75)%	<b>147</b> 81 (68) <sup>d</sup> %	<b>148</b> 68 (24)%	<b>149</b> >95 (76)%	<b>150</b> 44% <sup>e</sup> / 6% <sup>f</sup>
<b>151</b> 73 <sup>c,g</sup>	<b>152</b> 87 <sup>c,g</sup>	<b>153</b> 70 <sup>c</sup> (17)%	<b>154</b> 80 (47)%	<b>155</b> 51 (51)% <sup>g</sup>
	<b>156</b> 82 <sup>c</sup> (55)%	<b>157</b> 83 (76) <sup>d</sup> %		
<b>158</b> 68 (15)%	<b>159</b> 87 (80)%	<b>160</b> 93 (28)%	<b>161</b> 80 (32)%	
<b>162</b> (53)%	<b>163</b> 82 (77) <sup>d</sup> %	<b>164</b> <sup>h</sup>		

<sup>a</sup>Conditions: nitroarene (0.5 mmol),  $\text{NaBH}_4$  (20 equiv.) and  $\text{Fe}(\text{OTf})_3$  (10 mol%) were reacted in ethanol (0.13 M), r.t., 4 h. <sup>b</sup>Yield determined by  $^1\text{H}$  NMR spectroscopy using 1,3,5 trimethoxybenzene as internal standard. Isolated yield in parentheses. <sup>c</sup>1,2-Dichloroethane used as internal standard. <sup>d</sup>Isolated as the HCl salt. <sup>e</sup>Derived from 3-nitroaniline. <sup>f</sup>Derived from 1,3-dinitrobenzene. <sup>g</sup>Aniline (9%) also recovered. <sup>h</sup>Intractable mixture of products obtained.

The reactivity of various heterocycles functionalised with nitro groups were investigated under the developed reaction conditions (Table 3.4-3). 8-Nitroquinoline was successfully reduced to 8-aminoquinoline **164**. Interestingly, treatment of nitrosubstituted benzoxazole and benzothiazole derivatives with  $\text{NaBH}_4$  in the absence of an iron salt exclusively gave the reductively ring-opened product. However, in the presence of  $\text{Fe}(\text{OTf})_3$ , only the chemoselective reduction of the nitro group was observed to give amine-substituted benzoxazole and benzothiazole **165** and **166**. No identifiable products were isolated from the attempted reduction of 3-nitropyridine **167**.

**Table 3.4-3 Formal hydrogenation of nitro group functionalised heterocycles using Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub><sup>a,b</sup>**



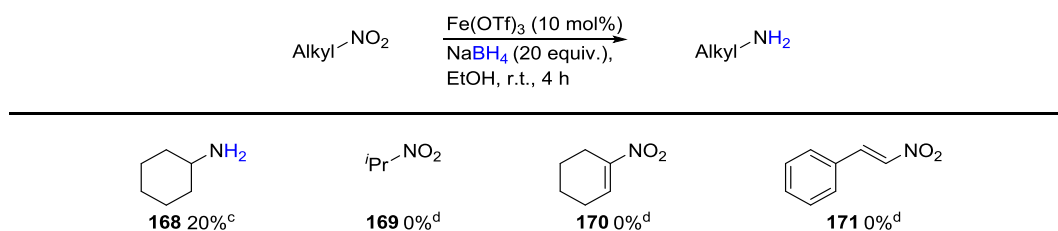
<sup>a</sup>Conditions: nitroheteroarene (0.5 mmol), NaBH<sub>4</sub> (20 equiv.) and Fe(OTf)<sub>3</sub> (10 mol%) were reacted in ethanol (0.13 M), r.t., 4 h. <sup>b</sup>Yield determined by <sup>1</sup>H NMR spectroscopy using 1,3,5 trimethoxybenzene as internal standard. Isolated yield in parentheses. <sup>c</sup>Intractable mixture of products recovered.

The majority of iron-catalysed nitro group reductions have been applied exclusively to nitroarenes, alkyl nitro groups have been investigated to a much smaller degree. Various nitro group substituted alkanes and alkenes were applied to the developed reaction conditions (Table 3.4-4).

Nitrocyclohexane was successfully reduced to aminocyclohexene **168** under the developed reaction conditions, however a maximum of only 20% yield could be achieved, even when Fe(OTf)<sub>3</sub> loading was increased to 50 mol% and that of NaBH<sub>4</sub> was increased to 30 equivalents. 2-Nitropropane **169** decomposed when exposed to Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub>, releasing a brown gas presumed to be NO<sub>x</sub> species.

Nitroalkenes were also assessed under the reaction conditions. Nitrocyclohexene **170** gave an intractable mixture of products and β-nitrostyrene **171** decomposed when exposed to the reaction conditions.

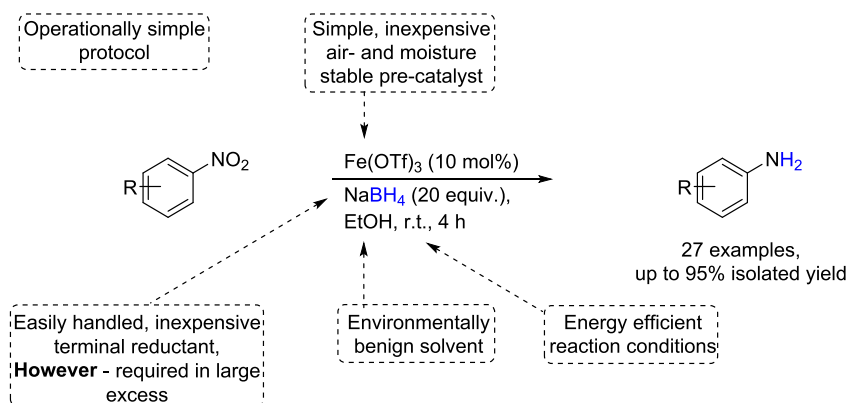


**Table 3.4-4 Formal hydrogenation of nitroalkanes and nitroalkenes using Fe(OTf)<sub>3</sub> and NaBH<sub>4</sub><sup>a,b</sup>**

<sup>a</sup>Conditions: nitroalkane or nitroalkene (0.5 mmol), NaBH<sub>4</sub> (20 equiv.) and Fe(OTf)<sub>3</sub> (10 mol%) were reacted in ethanol (0.13 M), r.t., 4 h. <sup>b</sup>Yield determined by <sup>1</sup>H NMR spectroscopy using 1,3,5 trimethoxybenzene as internal standard. <sup>c</sup>Fe(OTf)<sub>3</sub> (50 mol%), NaBH<sub>4</sub> (30 equiv.). <sup>d</sup>Starting materials decomposed under reaction conditions.

### 3.5 CONCLUSIONS

In summary, the operationally simple formal hydrogenation protocol using simple iron(III) salts and the air- and moisture stable stoichiometric reduction, NaBH<sub>4</sub>, has been expanded from use in alkene hydrogenations to a use in reducing the polar nitro group. A number of nitro substituted arenes and heteroarenes have been successfully reduced under environmentally benign reaction conditions (27 examples, up to 95% isolated yield). Practical conditions for the formal hydrogenation of nitroalkanes and nitroalkenes were unfortunately not successfully developed.

**Scheme 3.17** Summary of the formal hydrogenation of nitro groups developed in this work

The iron-catalysed reduction of nitroarenes and nitroheteroarenes discussed in this chapter has been published alongside the work presented in Chapter 2 (*Org. Biomol. Chem.* **2014**, 12, 5082-5088, DOI: 10.1039/C4OB00945B, see Appendix 1)

Further work on this project has been performed by various researchers in the Thomas group, and has focused on exploring the reactivity of other metal salts under these conditions, developing methods of reducing the NaBH<sub>4</sub> loading and expanding the substrate scope to further heterocycles.

# CHAPTER 4. IRON-CATALYSED ALKENE HYDROBORATION REACTIONS

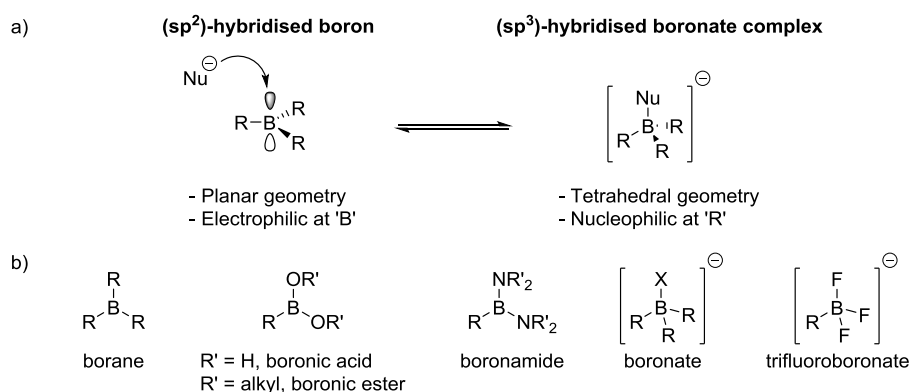
## 4.1 PREAMBLE

Chapter 4 consists of two major sections, the first of which is a background section detailing: the utility and therefore value of organoborane compounds; a brief overview of common syntheses of organoboranes including the hydroboration reaction; an overview of how the hydroboration reaction has been developed; and a comprehensive review of iron-catalysed hydroboration. A brief overview of chelating NHC ligands and the previously reported complexes thereof is included, along with the aims of this research project to develop the field of iron-catalysed hydroborations. The second section consists of the author's research: synthesising and characterising novel iron(II) NHC complexes; then developing two sets of reaction conditions to use these complexes for alkene hydroboration using catecholborane (HBcat) and pinacolborane (HBpin); finally mechanistic investigation into these reactions are presented.

## 4.2 INTRODUCTION

### 4.2.1 ORGANOBORANES IN ORGANIC CHEMISTRY

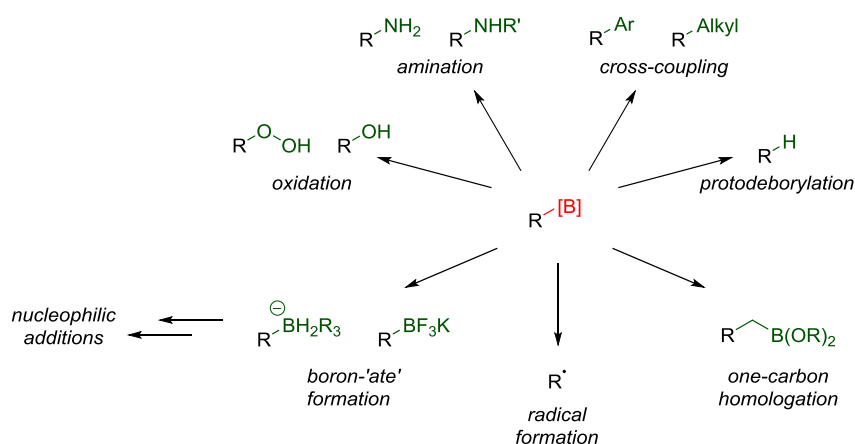
Organoboranes are among the most versatile reagents in organic synthesis.<sup>335,336</sup> In organoboron compounds, boron atoms typically adopt an oxidation-state of +3, and form 3 bonds to neighbouring atoms through ( $sp^2$ )-hybridised orbitals. Significantly, this leaves an vacant boron p-orbital, making the boron compounds highly electrophilic. Addition of nucleophiles into this orbital generates tetrahedral, ( $sp^3$ )-hybridised, anionic complexes. The ( $sp^3$ )-hybridised boronate complexes generated in this manner are nucleophilic on the groups coordinating boron. This switching between electrophilic and nucleophilic properties makes boron compounds extremely useful reagents in organic synthesis, lending themselves to a vast array of chemical transformations (Scheme 4.01 a).



**Scheme 4.01** a) The utility of organoboron reagents stems from the switchable, controllable, reactivity available at the boron centre. b) Selected nomenclature of relevant boron species used herein.

A wide range of organic transformations can be used to selectively transform organoboron reagents into an equally wide range of products. These transformations include, but are not limited to: protonolysis; oxidation to alcohols and peroxides;<sup>337</sup> the generation of alkyl- and aryl-radicals;<sup>338–340</sup> one-carbon homologation reactions;<sup>341,342</sup> and the generation and use of stable or transient boronate complexes (Scheme 4.02).<sup>343,344</sup>

Significantly, organoboranes are widely exploited as pro-nucleophiles in the extremely versatile Suzuki-Miyaura cross-coupling reaction to form C-C bonds. Suzuki-Miyaura reactions have become almost ubiquitous for compound discovery in medicinal chemistry,<sup>345</sup> and has been used in several very large scale syntheses including: the BASF synthesis of Boscalid on >1000 tonnes/year scale;<sup>346</sup> and the Merck synthesis of Losartan.<sup>347</sup> Indeed, so universal are Suzuki-Miyaura reactions, it has been suggested that the substrate scope of this reaction has led directly to stagnation in drug design.<sup>348</sup>



**Scheme 4.02** Selected transformations of organoboranes.<sup>337–341,343,344</sup>

#### 4.2.2 SYNTHESIS OF ORGANOBORANES

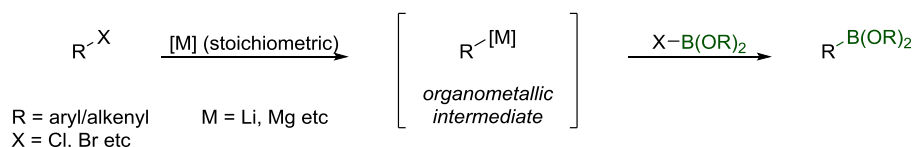
The utility of organoboron reagents is such that there are also myriad strategies for introducing boron-containing functional groups into organic molecules. In this section a brief overview and some recent examples of some of the most common are given.

A common method for the introduction of boron-containing functional groups is the reaction of boron species with organometallic reagents. This strategy typically involves metal-halogen exchange to generate a  $Mg^0$  or  $Li^0$  organometallic reagent which can then be quenched with an electrophilic boron reagent (Scheme 4.03 a).<sup>349</sup> While this reaction is powerful and allows access to numerous elegant syntheses,<sup>350,351</sup> it generates stoichiometric metals salts as byproducts and the functional group tolerance is often limited due to the high reactivity of organometallic reagents generated.

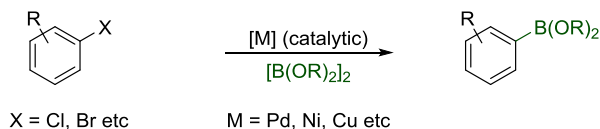
In a recent example of the organometallic introduction of boron species in conjunction with iron-catalysis, the Thomas group have also reported a hydromagnesiation protocol that generates benzylic Grignard reagents.<sup>352,353</sup> The resulting Grignard can be quenched with HBpin to selectively generate the branched hydroboration product.<sup>354</sup>

Catalytic strategies have been developed to exploit similar starting materials, particularly the 'Miyaura borylation', a Pd-catalysed cross-coupling reaction between aryl-halides and diboron reagents (Scheme 4.03 b).<sup>355,356</sup> The reaction has also been reported using Ni,<sup>357</sup> Cu,<sup>358</sup> and recently Fe.<sup>359,360</sup> These catalytic methods increase the step economy of a borylation reaction, as the production of a stoichiometric organometallic is not required, however the atom economy is still poor due to a stoichiometric byproduct being produced. Greater atom economy can be achieved by the exploitation of catalytic C-H activation strategies using precious metal, notably iridium, catalysts (Scheme 4.03 c).<sup>361–363</sup> While C-H activation has been developed in recent years into a powerful synthetic technique tuning the site-selectivity of the activation, is still challenging.<sup>363,364</sup> Techniques have also been developed to access borenium cations which are sufficiently electrophilic to be used as electrophiles in Friedel-Crafts type reactions (Scheme 4.03 d).<sup>365</sup> These reactions generate a stoichiometric amount of Brønsted acid byproducts, but significantly do not require a transition-metal catalyst.

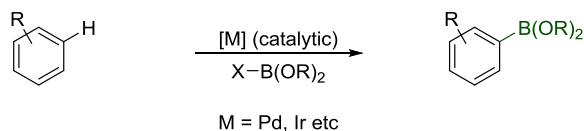
**a) Generation of stoichiometric organometallics from C-X bonds**



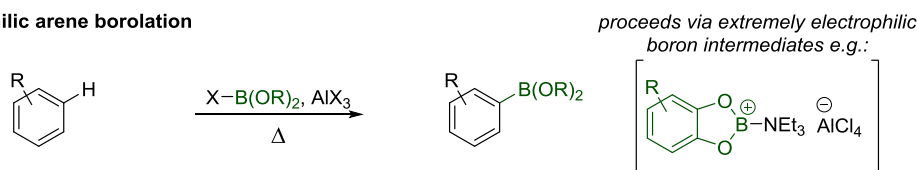
**b) Catalytic functionalisation of C-X bonds**



**c) Catalytic functionalisation of C-H bonds**



**d) Electrophilic arene borolation**



**Scheme 4.03** General schemes for ‘typical’ strategies for the introduction of boron-containing functional groups to organic molecules. a) generation and subsequent quenching of a stoichiometric organometallic reagent,<sup>349</sup> b) Miyaura borylation, in which metal catalyst activates a C-X,<sup>355,356</sup> c) C-H activation using a precious metal catalyst,<sup>361–363</sup> and d) electrophilic arene borylation.<sup>365</sup>

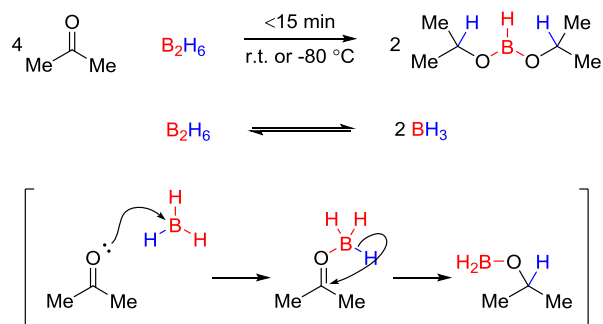
An alternative powerful technique for the introduction of boron moieties to organic molecules is that of alkene hydroboration. Hydroboration is a member of the family of hydrofunctionalisation reactions in which a hydrogen atom and another moiety are added across a multiple bond system (Section 1.2.3.1). These reactions are potentially extremely atom-economic, incorporating all atoms from the starting materials into the products. It is this technique which forms the majority of the work in this chapter, and which will be discussed in detail below.

## 4.2.3 ALKENE AND ALKYNE HYDROBORATION: GENERAL BACKGROUND

### 4.2.3.1 Early Work

The hydroboration reaction involves the addition of H-B bond across a C-X multiple bond. The earliest reported hydroboration reagent is diborane B<sub>2</sub>H<sub>6</sub>, first isolated by Stock in 1912.<sup>366</sup> Practical, albeit lengthy, syntheses of diborane, were later explored by the group of Schlesinger, who also investigated its reactivity with organic molecules.<sup>367,368</sup> Diborane was shown to be an extremely active reductant of carbonyl compounds (Scheme 4.04). Diborane exists in equilibrium with borane, and the reaction was proposed to proceed by coordination of the

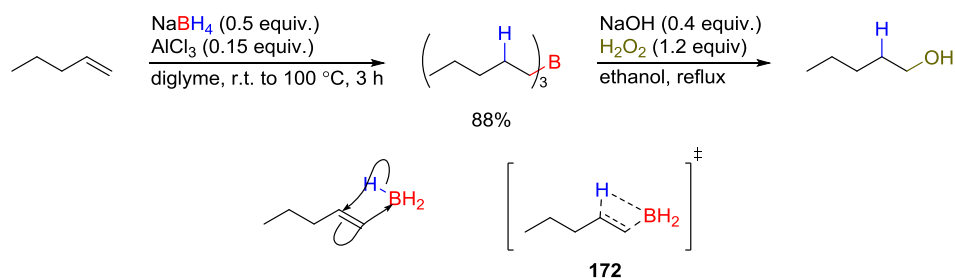
carbonyl lone-pair into the empty p-orbital on borane. The transient ‘activated’ boronate complex could then undergo hydride migration into the C-O double bond.



**Scheme 4.04** First report of the reactions between diborane ( $B_2H_6$ ) and organic molecules by H. Brown and Schlesinger in 1939 and the mechanism proposed.<sup>368</sup>

Following these reports, much of the early development of reagents containing silicon and boron hydrides was performed by the groups of Schlesinger and H. Brown on behalf of the United States Government’s uranium purification projects during World War II and led to the development of selective reductants such as  $NaBH_4$  and  $LiAlH_4$ .<sup>261,369,370</sup> During this work, the remarkable and notable difference in reactivity between the nucleophilic, charged borohydride derivatives and neutral, Lewis-acidic borane derivatives was first identified and exploited.

Diborane was demonstrated to also be a effective reagent for alkene hydroboration by the group of H. Brown (Scheme 4.05).<sup>371</sup> The addition of  $BH_3$  (and other hydroboration reagents) to alkenes and alkynes takes place in a concerted manner through a 4-membered transition-state structure **172** and due to boron being less electronegative than hydrogen, the reaction occurs in a characteristically *syn*-, *anti*-Markovnikov fashion. The alkyl-borane species generated by this reaction, which still contains B-H bonds and a vacant p-orbital, can undergo further alkene hydroboration reactions, generally generating trialkylborane complexes  $BR_3$ .



**Scheme 4.05** H. Brown’s 1956 hydroboration of alkenes, using  $BH_3$  generated in situ by treatment of  $NaBH_4$  with  $AlCl_3$ .<sup>371</sup>

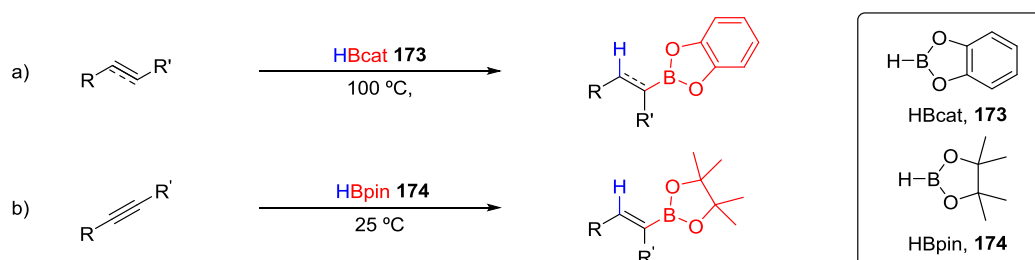
Various reagents and methodologies were developed to moderate this reactivity and selectively generate mono-, di- and cyclic- alkylboranes.<sup>372,373</sup> For example alkyl-borane reagent 9-

borabicyclo[3.3.1]nonane (9-BBN) which is commonly used in large scale synthetic applications both in academic,<sup>374,375</sup> and industrial settings.<sup>376</sup>

While versatile reagents, alkyl-boranes like 9-BBN are not air- or moisture stable and their reactivity can be challenging to control. This has led to the development of a number of borane-derived reagents whose reactivity is modulated by the incorporation of electron-donating substituents on boron. This commonly requires the formation of boronic esters, in which electron-donation from oxygen to the empty boron p-orbital decreases the electrophilicity of the boron centre.

Catecholborane, HBcat, **173** represents the first, commercially available, reagent capable of performing the hydroboration of alkenes to directly give alkyl-boronic ester products.<sup>377–379</sup> Catecholborane can be handled and stored in a pure form, and the alkene hydroboration products formed are typically air-stable albeit difficult to isolate and purify.<sup>380</sup> Catecholborane has proved to be an extremely useful and versatile reagent for both uncatalysed and metal-catalysed hydroboration reactions.

Pinacol boronic esters have been used to provide organoboranes with a high degree of stability (typically capable of tolerating column chromatography). These species were traditionally accessed by conversion *in situ* from other boron containing species.<sup>381</sup> Pinacolborane (HBpin) **174**, a reagent capable of performing alkene hydroboration to directly access the alkyl-, pinacol-boronic ester products was reported in the early 1990's by the group of Knochel (Scheme 4.06 b).<sup>382</sup> Pinacolborane was reported to hydroborate mono- and disubstituted alkynes, providing the (*E*)-vinylboronic esters in good yields and with high stereo- and regioselectivities. However work within the Thomas group has struggled to perform this reaction. Nevertheless, pinacolborane has become a highly valued reagent in organic synthesis.



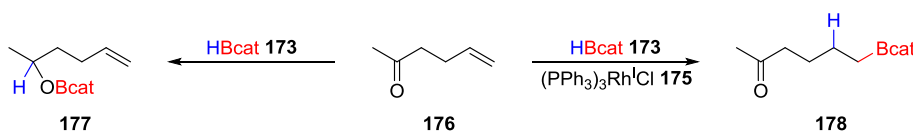
**Scheme 4.06** a) Uncatalysed hydroborations of alkenes and alkynes using HBcat **173**,<sup>377,378</sup> and b) uncatalysed hydroboration of alkynes using HBpin **174**.<sup>382</sup>

Fundamentally, all these reactions and their associated selectivities are under reagent control, the following section describes the development of catalysts which offer a further layer of control over alkene hydroboration reactions.

#### 4.2.3.2 Hydroboration Reactions Under Catalytic Control

Since catalytic hydroborations are mechanistically differentiated from uncatalysed reactions, catalytic hydroboration reactions offer the possibility of the chemo-, regio- and stereo-selectivity being defined by the catalyst selectivity rather than being under the substrate control, as they are in uncatalysed hydroboration reactions.<sup>383–385</sup>

While early catalytic hydroboration reactions required the use of synthetically intractable polymeric boron hydrides,<sup>386,387</sup> a key breakthrough in this field was the reports of oxidative addition of Rh<sup>I</sup> complexes into H-B bonds.<sup>388</sup> Männig and Nöth published the use of Wilkinson's catalyst ( $[\text{PPh}_3]_3\text{Rh}^{\text{I}}\text{Cl}$  **175**)<sup>389</sup> to promote the otherwise rather sluggish hydroboration of 5-hexen-2-one **176** with catecholborane.<sup>390</sup> Under uncatalysed conditions, HBcat is selective for carbonyl reduction to give **177** over alkene hydroboration, however the use of Wilkinson's catalyst **175** completely switched the chemoselectivity of the reaction to give **178** (Scheme 4.07). A number of other precious-metal complexes, including iridium(I) complexes and cationic rhodium(I) complexes were rapidly discovered to be active for alkene hydroboration using HBcat.<sup>383</sup>



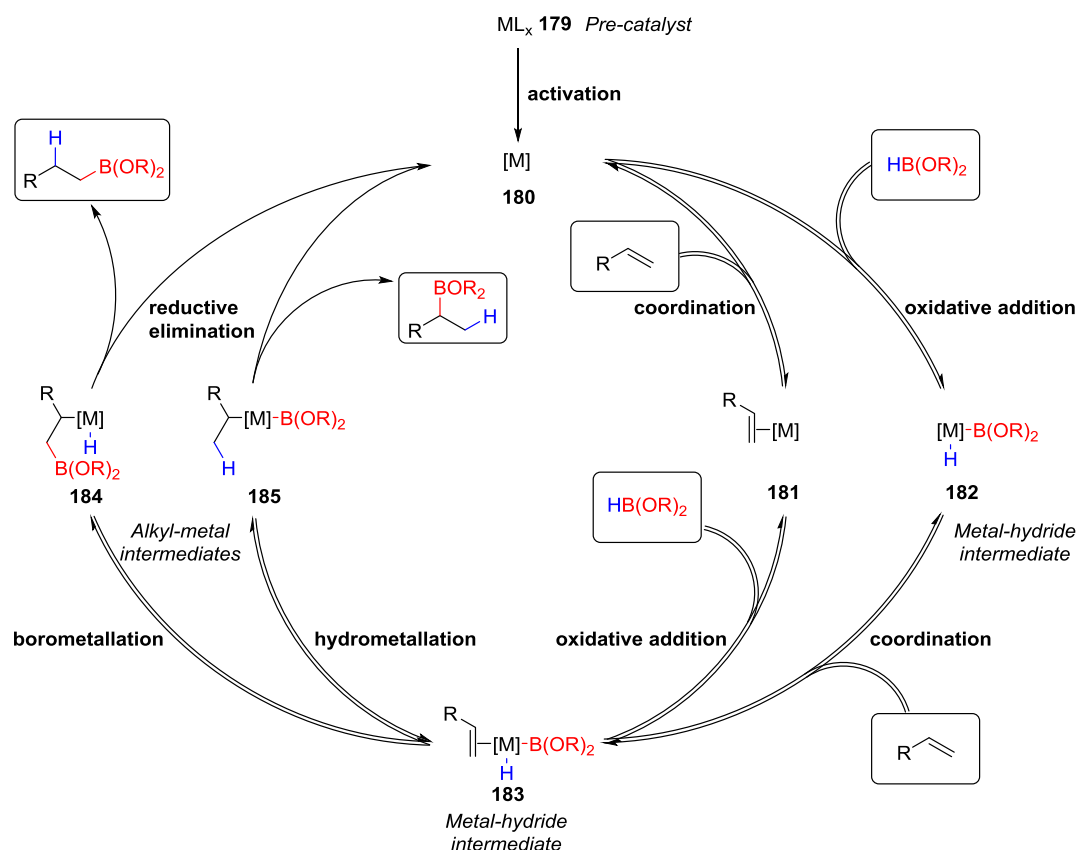
**Scheme 4.07** Switch of chemoselectivity in the hydroboration with HBcat in the presence and absence of Wilkinson's catalyst  $(\text{PPh}_3)_3\text{Rh}^{\text{I}}\text{Cl}$  **173** as reported by Männig and Nöth.<sup>390</sup>

The mechanism by which rhodium-catalysed hydroborations with HBcat proceed was established by mechanistic studies by the groups of Evans and Fu,<sup>391,392</sup> and computational methods,<sup>393–395</sup> especially that of Ziegler and co-workers.<sup>396</sup> The general mechanism for (redox active) transition-metal-catalysed hydroboration is analogous to the Chalk-Harrod mechanism,<sup>397</sup> and modified Chalk-Harrod mechanism,<sup>398–400</sup> active in hydrosilylation reactions (Scheme 4.08).

A typical catalytic cycle starts with the activation of a pre-catalyst **179** to an active catalytic species **180**. For example, in the hydroboration of ethylene with HBcat using Wilkinson's catalyst **175**, catalyst activation occurs by dissociation of a phosphine ligand to generate a vacant coordination site. The activated catalyst can then undergo one of two processes, either: coordination of an alkene to give intermediate **181**; or an oxidative addition into HBpin give metal-hydride intermediate **182**. These two intermediates typically converge on the key intermediate **183**, with the alkene, hydride and Bcat coordinated to the metal centre. In the example of ethylene with Wilkinson's catalyst, this key intermediate requires the hydride and Bcat to be coordinated in a *trans*- fashion to allow the following metallation step to occur. This

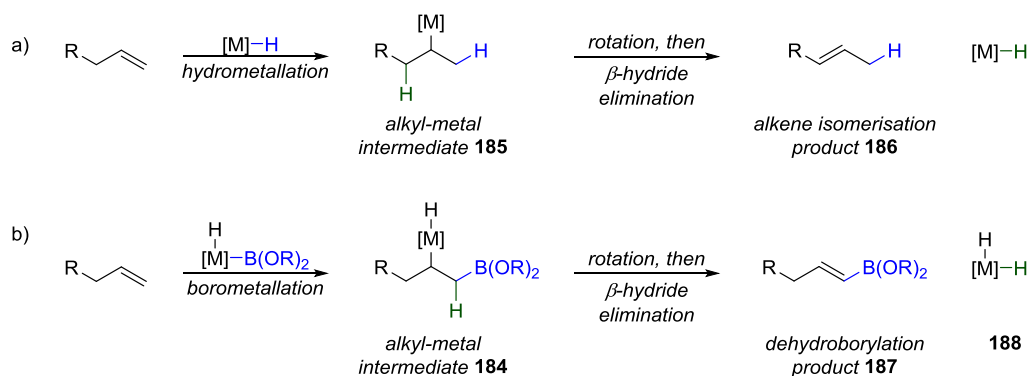


intermediate **183** can then undergo either a borometallation or hydrometallation to generate alkyl- metal intermediates **184** and **185**. Finally, a reductive elimination step regenerates the active catalytic species **180** and releases the hydroboration product(s).



**Scheme 4.08** General catalytic cycle for metal-catalysed hydroborations of unsaturated hydrocarbons.

Divergence from this catalytic cycle results in the formation of side products. Commonly encountered in alkene hydroboration reactions are alkene isomerisation reactions, to give **186**, occurring by  $\beta$ -hydride elimination from the alkyl- metal intermediate **185** (Scheme 4.09 a). Additionally,  $\beta$ -hydride elimination from the alkyl- metal intermediate **184** generates the dehydrogenative borylation product **187** along with a dihydrometal species **188** (Scheme 4.09 b). Dihydrometal species are typically active hydrogenation catalysts, meaning that a dehydrogenative borylation product is usually accompanied by a stoichiometric quantity of an hydrogenation product.

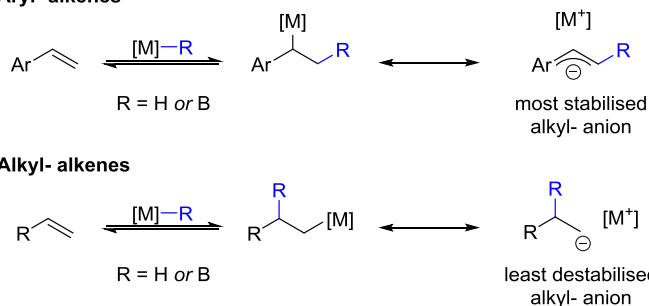


**Scheme 4.09** Divergence from the catalytic cycle at key alkylmetal intermediates **185** and **184** leads to the formation of side products.

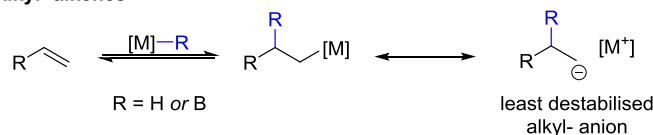
The key step for determining product regioselectivity is the selectivity between hydrometallation and borometallation to form alkylmetal intermediate **184** or **185**. The regioselectivity of the formation of the alkylmetal intermediates has a strong substrate dependence. Substrates in which an alkyl anion can be stabilised, most often arylalkenes, have an intrinsic selectivity for forming the alkylmetal intermediate at the most electronically stabilised position, which proceeds to give products **189** and **190**. Alkylalkenes generate the alkylmetal intermediate at the least sterically encumbered position, which proceeds to give products **191** and **192** (Scheme 4.10). The regioselectivity of the hydroboration reaction is therefore determined by the regioselectivity of the metallation reaction, which is substrate dependent, and selectivity for hydro- or borometallation which is dependent on both the catalyst and the hydroboration reagent. In cases in which these events are similar in energy, poor selectivity is observed. This makes catalyst design and substrate choice vital for achieving high selectivities. Additionally designing catalysts able to overcome the intrinsic selectivity of a substrate or substrate class can remain challenging.

**Favoured alkyl-metal intermediates:**

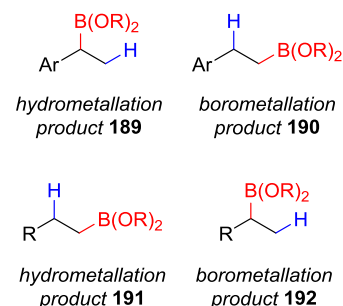
a) **Aryl- alkenes**



b) **Alkyl- alkenes**



**Products:**



**Scheme 4.10** Reversal in intrinsic substrate-determined selectivity for the formation of alkyl- metal intermediates and the product selectivity as a result.

In the hydroboration of styrene **193**, Wilkinson's catalyst **175** in conjunction with HBcat shows extremely high regioselectivity for the branched hydroboration product **194** (Table 4.2-1, Entry

1). Although it should be noted that the reported selectivity of this reaction was for some time confused by oxidation of the rhodium complexes promoting the linear hydroboration reactions,<sup>401</sup> and in some cases the decomposition of HBcat to BH<sub>3</sub> promoted by free phosphine ligands.<sup>402</sup> This highlights the importance of using freshly-prepared Wilkinson's catalyst in hydroboration reactions.

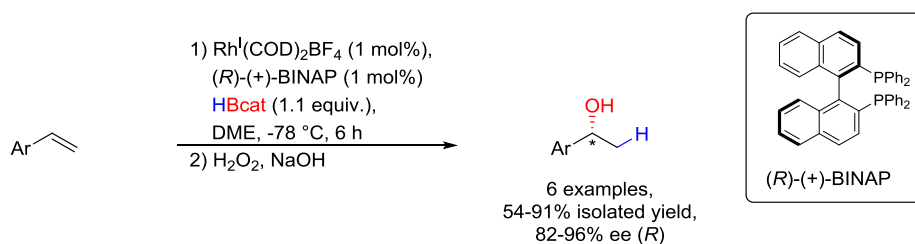
When used with HBpin, Wilkinson's catalyst gives non-synthetically useful mixtures of branched **194** and linear **195** hydroboration products along with dehydrogenative borylation product **196** (Entry 2). Good selectivity for the branched hydroboration product **194** with HBpin can be achieved by using cationic Rh<sup>I</sup> complexes with weakly coordinating counterions and bidentate phosphine ligands (Entry 3).<sup>403–405</sup> It should however be noted that these complexes are not commercially available. Ir<sup>I</sup> complexes, which are also well established for alkene hydroboration, react with styrene derivatives to give exclusively the linear hydroboration product (Entry 4).

**Table 4.2-1 Previously reported regioselective of Rh and Ir catalysed hydroboration of styrene.**<sup>403</sup>

Entry	[M] (mol%)	HB(OR) <sub>2</sub>	Yield (%)		
			Branched product <b>194</b>	Linear product <b>195</b>	Dehydrogenative borylation product <b>196</b>
1	(Ph <sub>3</sub> P) <sub>3</sub> Rh <sup>I</sup> Cl (2)	HBcat	>99	1	-
2	(Ph <sub>3</sub> P) <sub>3</sub> Rh <sup>I</sup> Cl (5)	HBpin	20-35	50-60	15
3	Rh <sup>I</sup> (COD) <sub>2</sub> BF <sub>4</sub> /DPPB (5)	HBpin	71	1	-
4	[Ir <sup>I</sup> (COD)Cl] <sub>2</sub> /DPPB (5)	HBpin	1	99	-

DPPB = 1,4-bis(diphenylphosphino)butane.

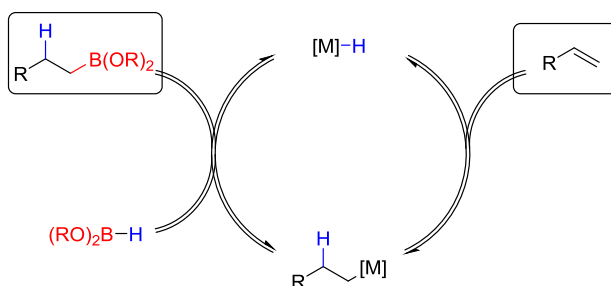
As well as excellent chemo- and regioselectivity, rhodium-catalysed alkene hydroboration reactions have been used to obtain excellent enantioselectivities.<sup>383</sup> To choose one example from many, Hayashi et al have reported the hydroboration of styrene derivatives using cationic Rh<sup>I</sup> complexes with axially chiral BINAP ligands and HBcat.<sup>406</sup> When the reaction was performed at -78 °C, good regio- and enantioselectivities could be achieved.



**Scheme 4.11** Selected example of Markovnikov-selective  $\text{Rh}^{\text{I}}$ -catalysed hydroboration of styrene derivatives with good enantioselectivities, reported by Hayashi *et al.*<sup>406</sup>

The differing sterics and electronics of HBcat and HBpin result in variation in yields and selectivities.<sup>407</sup> Examples of branched-selective hydroboration of styrene derivatives using HBpin with good enantioselectivity have been achieved, albeit typically with eroded regioselectivity or yield.<sup>403,408,409</sup> Interestingly, chiral  $\text{Rh}^{\text{I}}$  complexes have been reported to induce a reversed sense of enantioselectivity when moving from HBcat to HBpin.<sup>403</sup>

It should be noted that metal-catalysed hydroboration reactions have also been reported using strong Lewis acids, such as lanthanides or titanium(II) and zirconium(II) complexes. These complexes typically perform the hydroboration of alkenes in an *anti*-Markovnikov manner, proceeding around a redox-neutral catalytic cycle (Scheme 4.12).<sup>383</sup>



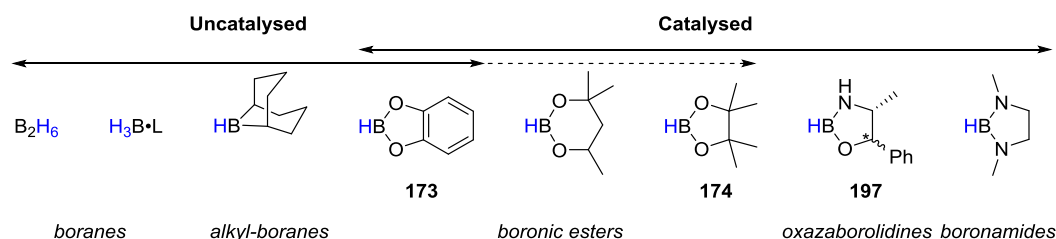
**Scheme 4.12** General catalytic cycle for Lewis-acid (redox neutral) metal-catalysed hydroboration of alkenes.

#### 4.2.3.3 Recent Developments in Metal-Catalysed Hydroboration Reactions

To summarise, in the 60 years between the 1930's and 1990's, borane reagents and their reactions with organic molecules went from being an obscure curiosity, to one of the cornerstones of modern organic chemistry.

The hydroboration reaction has a wide range of reagents associated with it, each of which exhibits particular properties, allowing the reaction to be tailored to given substrates and conditions (Figure 4.01). Boranes, alkylboranes and some boronic esters such as **173** perform the hydroboration of alkenes in the absence of a catalyst. Boronic ester and boronamide reagents have been reported for numerous metal-catalysed alkene hydroborations. Of these, only HBcat **173** and HBpin **174** are readily commercially available, and so form the vast bulk of

reported examples.<sup>384</sup> The group of J. Brown has reported the use of chiral hydroboration reagents **197** derived from ephedrine and pseudoephedrine, in conjunction with Wilkinson's Catalyst **175** in order to perform enantioselective alkene hydroborations.<sup>410</sup>



**Figure 4.01** Selected boron reagents reported for alkene hydroboration reactions.

Despite the considerable work that has been put into precious metal-catalysed alkene hydroboration reactions, examples of industrial exploitation of this reaction are rare. This is in stark contrast to both the widely exploited uncatalysed hydroboration,<sup>374–376</sup> and the ubiquity of the closely-related hydrosilylation reaction which is arguably one of the most commercially important consumers of platinum.<sup>108</sup> This is presumably due to the use of expensive and scarce metals as catalysts, along with operationally complex reaction conditions.

In light of this, and the general trend towards the use of more environmentally benign systems in synthetic chemistry,<sup>5,6</sup> in recent years there has been a push towards developing inexpensive, sustainable and non-toxic metal catalysts for alkene hydroboration. This has led to a spate of publications in recent years detailing hydrofunctionalisation reactions utilising first-row transition metals as catalysts. Alkene hydroboration reactions catalysed by iron complexes are detailed below.

It is also interesting to note that there have also been organocatalytic examples of hydroborations published, most notably using Lewis bases to perform the hydroborations of alkenes using HBCat **173**, although the mechanism is far from clear.<sup>411</sup>

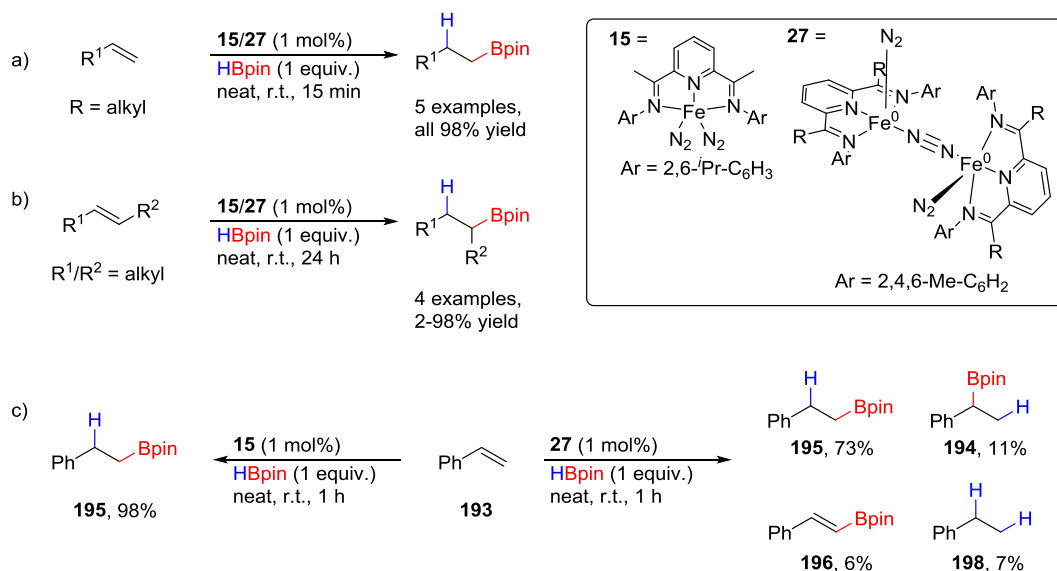
#### 4.2.3.4 Iron-Catalysed Alkene Hydroboration Reactions

In keeping with other aspects of iron-catalysis, the number of reports of iron-catalysed hydroboration reactions has increased dramatically in recent years.

Chirik and co-workers have reported a family of complexes of the general formula  $\text{BIPFe}^0(\text{N}_2)_n$  (*vide supra*), these highly air- and moisture sensitive complexes have been demonstrated to be highly active pre-catalysts for a range of [2+2] cycloaddition,<sup>412,413</sup> hydrogenation,<sup>223,224</sup> and hydrosilylation reactions.<sup>414</sup> Given the mechanistic similarities between hydrosilylation and hydroboration, it is unsurprising that these complexes have also been reported to be active for

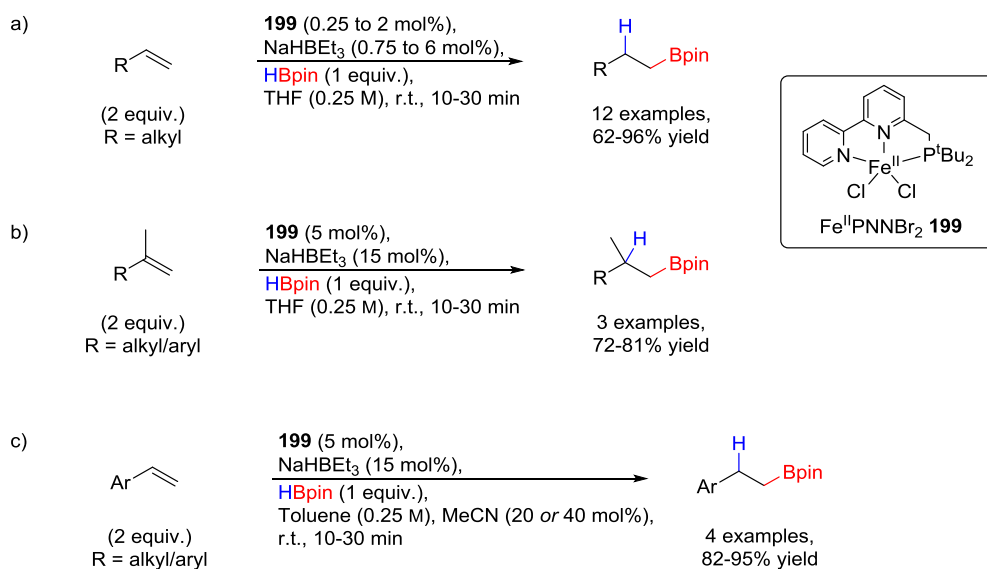
the hydroboration of terminal alkenes (4 examples, all 98% yield, Scheme 4.13 a), internal alkenes (4 examples, 2-98% yield, Scheme 4.13 b).<sup>415</sup>

Interestingly, Chirik and co-workers demonstrated that for an aryl-substituted alkene substrate (styrene **193**) relatively minor changes in the steric bulk of the complexes from  $^{n\text{Pr}}\text{BIPFe}^0(\text{N}_2)_2$  **15** to  $[\text{MesBIPFe}^0(\text{N}_2)]_2(\text{N}_2)$  **27** could dramatically change the selectivity from exclusively linear hydroboration to a mixture of linear and branched hydroboration products **195** and **194**, dehydrogenative borylation product **196** and the hydrogenation product **198** (Scheme 4.13 c).



**Scheme 4.13**  $\text{BIPFe}^0(\text{N}_2)_n$  complexes **15** and **27** for a) alkene hydroboration and b) alkyne hydroboration, c) switch of selectivity with changing sterics on the complex.<sup>415</sup>

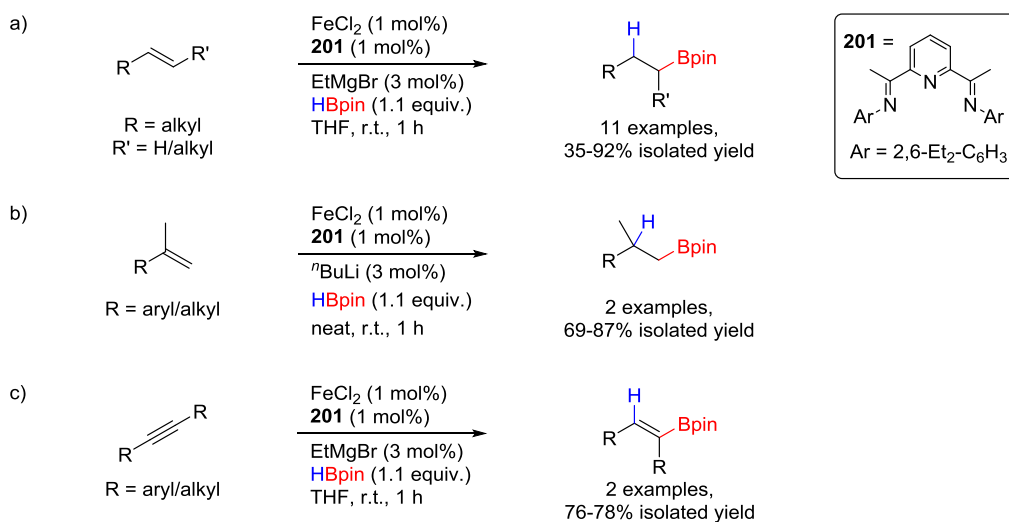
Huang and co-workers have screened a number of iron(II) chloride complexes supported by multidentate N-donor ligands, activated *in situ* with  $\text{NaHBET}_3$  for alkene hydroboration. Under these conditions,  $\text{PNNFe}^{\text{II}}\text{Cl}_2$  **199** was more active than  $^{n\text{Pr}}\text{BIPFe}^{\text{II}}\text{Cl}_2$  **15**,  $\text{TERPYFe}^{\text{II}}\text{Cl}_2$  **200** and an iminopyridine- $\text{FeCl}_2$  complex, previously reported by Ritter for diene hydroboration (*vide infra*).<sup>416</sup> Alkyl-substituted alkenes could be transformed to the linear hydroboration product (12 examples, 62-96% yield, Scheme 4.14 a) as could 1,1-disubstituted alkenes (3 examples, 72-81% yield, Scheme 4.14 b). Styrene **193** resulted in a mixture of dehydrogenative borylation (65% yield relative to HBPIn) and hydrogenation (21% yield) products in addition to the linear hydroboration product **195** (34% yield). The hydroboration of styrene derivatives could be successfully achieved by moving to a toluene/acetonitrile solvent mixture (4 examples, 80-95% yield, Scheme 4.14 c).



**Scheme 4.14** PNNFe<sup>II</sup>Cl<sub>2</sub> **199** complexes for alkene hydroboration.<sup>416</sup>

The group of Thomas have reported a hydroboration reaction using an air- and moisture stable pre-catalyst, synthesised from FeCl<sub>2</sub> and EtBIP **201**, activated *in situ* with an organometallic reagent (either EtMgBr or <sup>n</sup>BuLi).<sup>417</sup> The reaction protocol was applied to the hydroboration of terminal and 1,2-disubstituted alkenes (11 examples, 35-92% isolated yield, Scheme 4.15 a), 1,1-disubstituted alkenes (2 examples, 69-87% isolated yield, Scheme 4.15 b) and internal alkynes with excellent stereoselectivity for the (*Z*)-vinyl boronic ester products (2 examples, 76-78% isolated yield, Scheme 4.15 c). The reaction proceeded rapidly at room temperature, in either THF or toluene solvents or neat. Tolylmagnesium bromide could also be used to activate the catalyst, and quantification by <sup>1</sup>H NMR spectroscopy of the bitolyl formed was used to infer the oxidation state of the active iron catalyst. This showed that the average oxidation-state of iron species in the reaction mixture was Fe<sup>I</sup>, a catalytic intermediate that has been implicated in a wide range of iron mediated cross-coupling reactions.<sup>48</sup> However, more recent work has suggested that the quantification of reductive elimination products is often not an accurate metric for the oxidation state for iron-catalysts.<sup>418</sup>

The Thomas group have demonstrated that these conditions are also viable for the hydrosilylation,<sup>419</sup> and hydrogermylation of alkenes.<sup>417</sup> Unfortunately, attempts to produce an effective enantioselective hydrofunctionalisation reaction by using chiral amines to construct unsymmetric BIP ligands proved to be unsuccessful.<sup>420</sup>

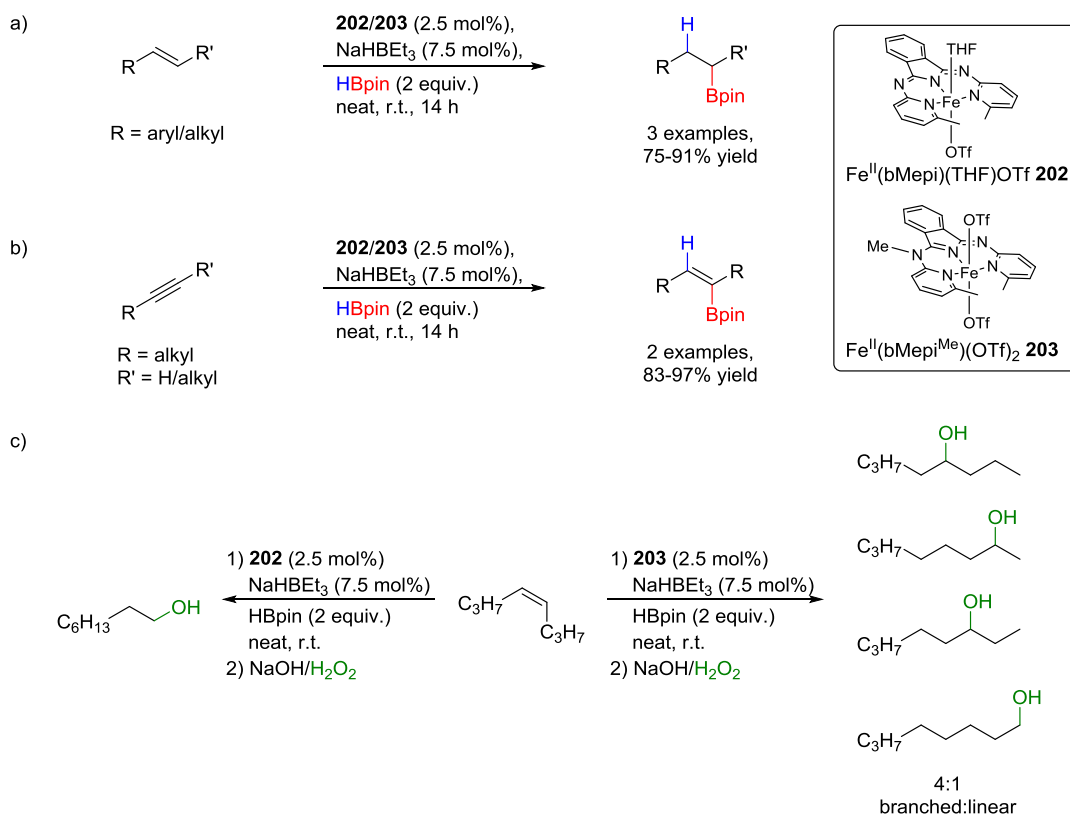


**Scheme 4.15** Thomas' hydroboration of linear and 1,1-disubstituted alkenes and internal alkynes using  $\text{EtBIPFe}^{\text{II}}\text{Cl}_2$  complex activated by organometallics.<sup>417</sup>

The group of Szymczak have reported iron(II) complex  $\text{Fe}^{\text{II}}(\text{bMepi})(\text{THF})\text{OTf}$  **202** bearing the anionic  $N,N,N$ -1,3-bis(6'-methyl-2'-pyridylimino)isoindolate (bMepi) ligand, and  $\text{Fe}(\text{bMepi}^{\text{Me}})(\text{OTf})_2$  **203** bearing the methylated, neutral analogue of the ligand. These complexes, when activated *in situ* by organometallic reagent  $\text{NaHBET}_3$ , were active for the hydroboration of alkenes (3 examples, 75-91% isolated yield, Scheme 4.16 a) and alkynes (2 examples, 83-97% isolated yield, Scheme 4.16 b).<sup>421</sup>

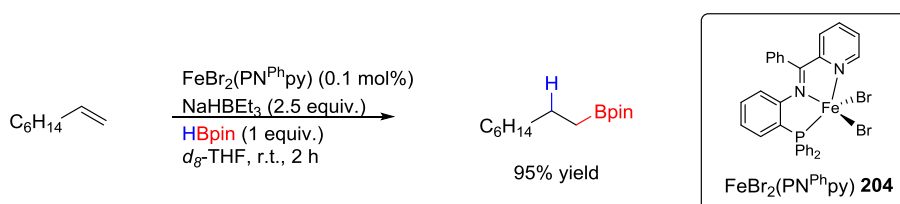
An interesting change in selectivity was observed for internal alkene *cis*-4-octene (Scheme 4.16 c) whereby complex **202** gives the thermodynamic product following chain walking, whereas complex **203** results in a mixture of branched and linear product.





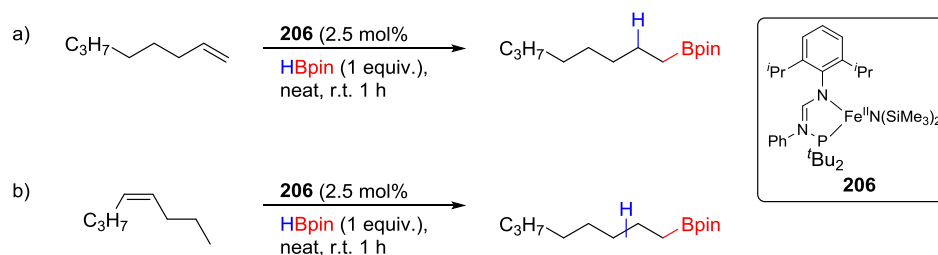
**Scheme 4.16** Szymczack's **202** or **203** catalysed hydroboration of a) alkenes and b) alkynes, along with c) the observed change in selectivity with *cis*-4-octene.<sup>421</sup>

The group of Rauchfuss have investigated the synthesis of iron(II) complexes supported by phosphine-imine-pyridine ligands. Complex  $(\text{PN}^{\text{Ph}}\text{py})\text{Fe}^{\text{II}}\text{Br}_2$  **204** was demonstrated to be active for the linear hydrosilylation and hydroboration of 1-octene, when activated *in situ* by  $\text{NaHBEt}_3$  (2.5 equivalents relative to alkene) (Scheme 4.17).<sup>422</sup>



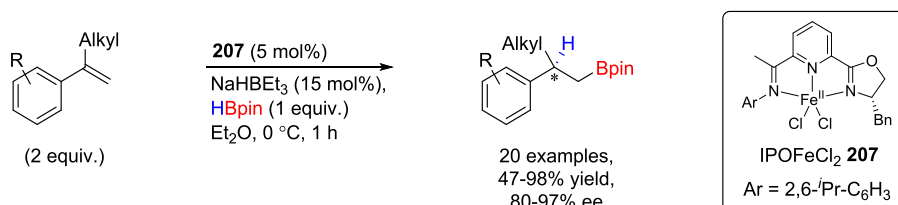
**Scheme 4.17** Rauchfuss' linear hydroboration of octene using  $(\text{PN}^{\text{Ph}}\text{py})\text{Fe}^{\text{II}}\text{Br}_2$  **204**.<sup>422</sup>

The groups of Stradiotto and Turculet have reported a novel bidentate *P,N*-donor ligand and the corresponding  $\text{LCo}^{\text{II}}\text{N}(\text{SiMe}_3)_2$  and  $\text{Fe}^{\text{II}}\text{N}(\text{SiMe}_3)_2$  complexes **205** and **206**. Iron complex **206** was demonstrated to be active, in the absence of any external activator, for the hydroboration of both 1-octene and 3-octene, to give the linear hydroboration product in both cases.<sup>423</sup>



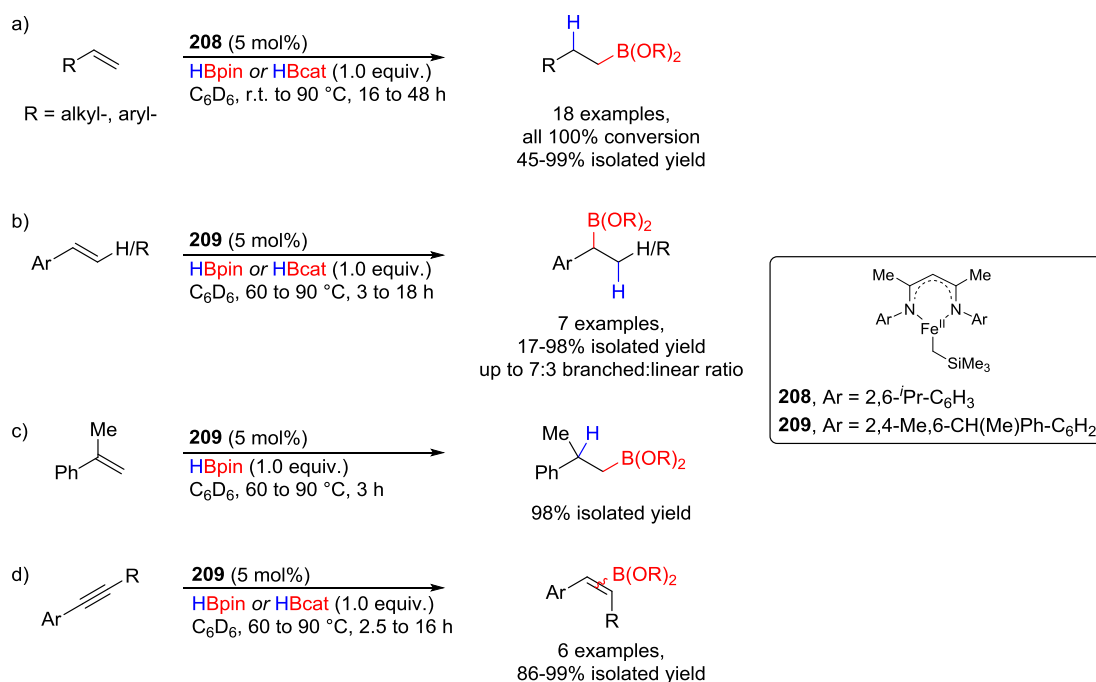
**Scheme 4.18** Novel iron(II) complexes, active in the absence of any external activator for the linear-selective hydroboration of 1- and 3-octene.<sup>423</sup>

Lu and co-workers have reported the first example of an enantioselective iron-catalysed alkene hydroboration reaction.<sup>424</sup> This reaction uses an iminopyridine oxazoline (IPO) ligand supported iron(II) chloride complex IPOFe<sup>II</sup>Cl<sub>2</sub> **207**, activated *in situ* by NaHBET<sub>3</sub>, which is active for the *anti*-Markovnikov selective hydroboration of 1,1-disubstituted styrene derivatives, with good regio- and enantioselectivities (20 examples, 47-98% isolated yield, 80-97% *ee*, Scheme 4.19). IPOFe<sup>II</sup>Cl<sub>2</sub> complex **207** has also been reported to be active, under extremely similar conditions, for the regio- and enantioselective hydrosilylation of 1,1-disubstituted alkenes.<sup>425</sup>



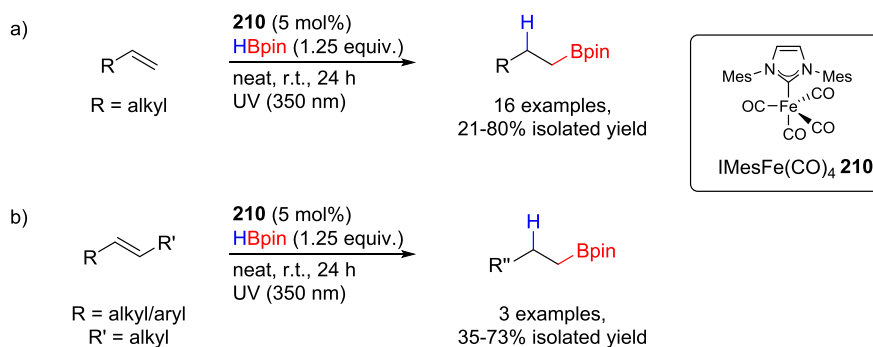
**Scheme 4.19** Lu's enantioselective hydroboration of 1,1-disubstituted alkenes.<sup>425</sup>

The group of Webster has reported the hydroboration of alkenes and alkynes with HBpin and HBcat using  $\beta$ -diketiminate complexes **208** and **209** (Scheme 4.20).<sup>426</sup> Complex **208** catalyses the *anti*-Markovnikov selective hydroboration alkyl- and aryl substituted alkenes with both HBpin and HBcat (17 examples, 45-99% isolated yield). Complex **209** catalyses the *anti*-Markovnikov selective hydroboration for  $\alpha$ -methylstyrene, and the Markovnikov selective hydroboration of unsubstituted- and  $\beta$ -substituted styrene derivatives (7 examples, 71-98% isolated yield, up to 7:3 branched:linear selectivity). Alkynes proved to be successful substrates for hydroboration with complex **209** (6 examples, 86-100% isolated yield).



**Scheme 4.20** Hydroboration of alkenes and alkynes by  $\beta$ -diketiminate complexes **208** and **209** reported by the group of Webster.<sup>426</sup>

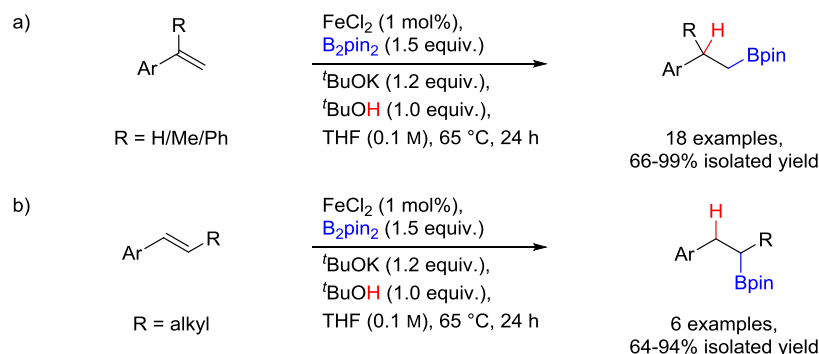
Unlike all the previously discussed examples, which utilise multidentate *N*-donor ligands, Darcel and co-workers have reported an NHC iron(0) carbonyl complex IMesFe(CO)<sub>4</sub> **210** for the *anti*-Markovnikov hydroboration of terminal (16 examples, 21-80%, Scheme 4.21 a) and internal (3 examples, 35-73%, Scheme 4.21 b).<sup>427</sup> A significant drawback for this system is the requirement for constant UV irradiation for catalyst activation.



**Scheme 4.21** IMesFe<sup>0</sup>(CO)<sub>4</sub> complex **210** active for the *anti*-Markovnikov selective hydroboration of terminal and internal alkenes.<sup>427</sup>

The group of Zhou has reported the *anti*-Markovnikov-selective formal hydroboration of styrene derivatives, including examples with 1,1- and 1,2-disubstitution (24 examples, 64-99% isolated yield, Scheme 4.22).<sup>428</sup> The optimised reaction conditions were reported to be: using: iron(II) chloride (1 mol%); B<sub>2</sub>pin<sub>2</sub> (1.5 equiv.), *tert*-butoxide (1.2 equiv.) and *tert*-butanol (1.0 equiv.) in THF at 65 °C for 24 h. The researchers propose that the reaction proceeds by the

formation of a boronate complex, which can transmetallate with iron, to give a boryliron complex. Borylmetallation of the alkene can lead to a alkyliron intermediate, and the use of a deuterated alcohol, showed that the catalytic cycle is turned-over by protonation of this species.



**Scheme 4.22** Formal hydroboration of vinylarenes reported by the group of Zhou.<sup>428</sup>

With the first publications on iron-catalysed hydroborations only appearing in 2013, rapid progress has been made in this field including, notably, stereo- and enantioselective systems. It should be noted however, that most of the systems discussed above have several features in common: low oxidation-state iron or iron(II) reduced *in situ*; imino-pyridine ligand motifs; and the use of pinacolborane as the hydroboration agent.

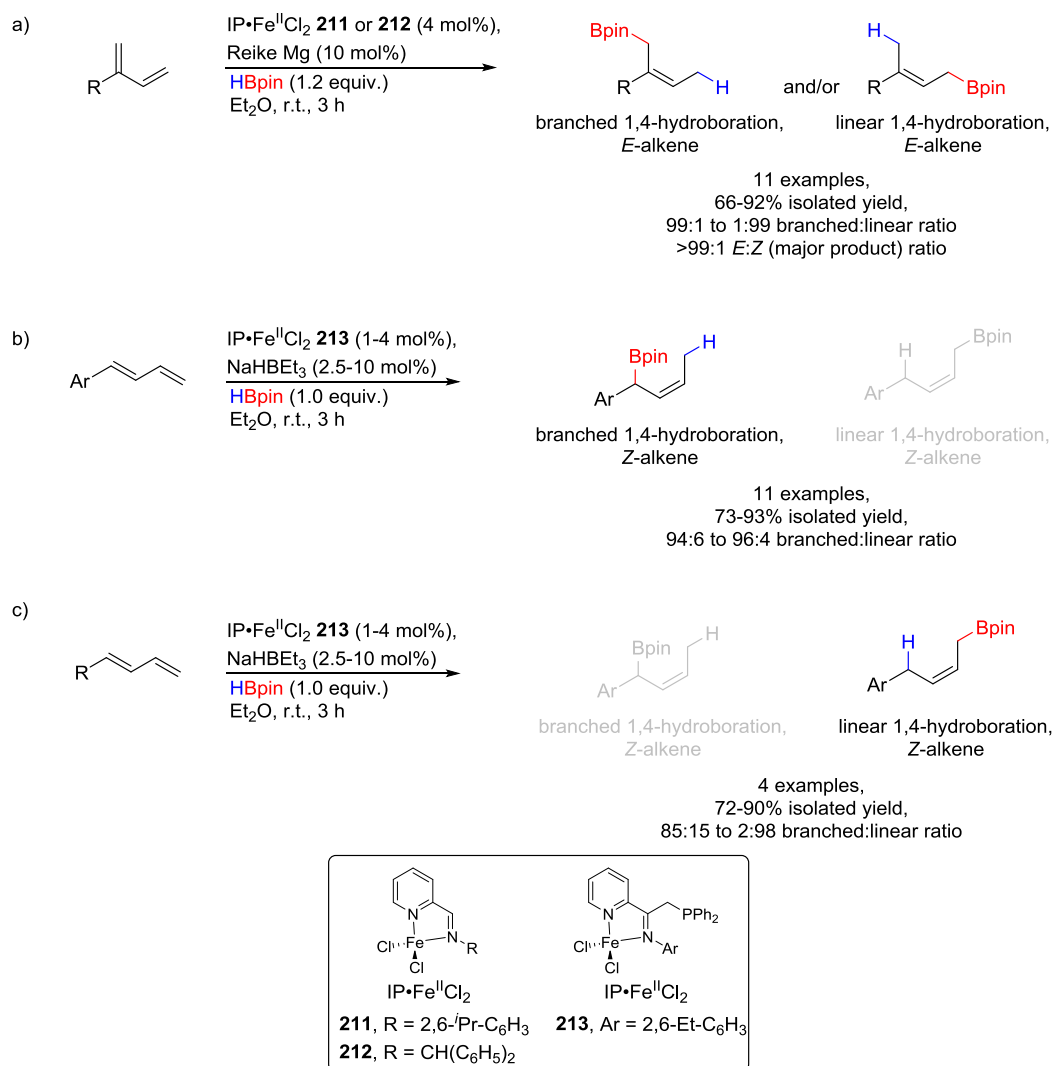
#### 4.2.3.5 Iron-Catalysed Diene Hydroboration Reactions

Ritter and co-workers have reported iminopyridine iron(II) chloride complexes **211** and **212**, activated *in situ* with highly-reactive Reike magnesium, active for the 1,4-hydroboration of 1,3-dienes (11 examples, 62-92% yield, 99:1 to 1:99 branched:linear ratio, Scheme 4.23 a).<sup>429</sup> Ligand sterics could be used to modulate the branched/linear selectivity of the reaction, allowing controlled, switchable up to 99:1 regioselectivity. The (*E*)-alkene product was exclusively formed.

The group of Ritter have previously reported iminopyridine iron(II) complexes for diene hydrosilylation.<sup>430,431</sup> In this case, a well-defined air- and moisture sensitive bis(aryl) iron(II) complex is formed from the reaction between the iron(II) chloride and aryl-lithium reagents. This complex can then be triggered into undergoing reductive elimination by the addition of iminopyridine ligands to generate *in situ* an active low oxidation-state diene hydrosilylation catalyst.

The group of Huang have performed an extensive screen of IPFe<sup>II</sup>Cl<sub>2</sub> complexes, activated *in situ* by NaHBEt<sub>3</sub>, for the 1,4-hydroboration of 1,3-dienes.<sup>432</sup> Complex **213** was found to be active for the selective hydroboration of aryl-substituted 1,3-dienes giving the branched regioisomer as the primary product and, in contrast to the results of Ritter and co-workers,

selective exclusively for the (*Z*)-alkene (11 examples, 73-93% isolated yield, 94:6 to 96:4 branched:linear ratio, Scheme 4.23 b). Alkyl-substituted 1,3-dienes selectively formed the linear product, again with (*Z*)-alkene selectivity (4 examples, 72-90% yield, 85:15 to 2:98 branched:linear ratio, Scheme 4.23 c). This switch in selectivity highlights the importance of substrate stabilisation of the alkyl-iron catalytic intermediate in determining the branched/linear selectivity of the reaction.

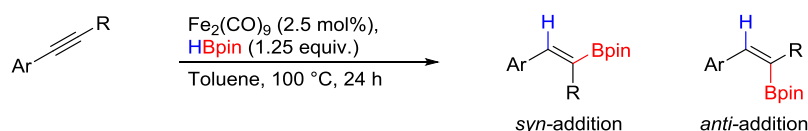


**Scheme 4.23** Iminopyridine complexes as active diene hydroboration catalysts reported by a) Ritter and co-workers, activated with Reike magnesium,<sup>429</sup> and b) Huang and co-workers activated with NaHBEt<sub>3</sub>.<sup>432</sup>

#### 4.2.3.6 Iron-Catalysed Alkyne Hydroboration Reactions

Iron-catalysed alkyne hydroboration reactions proceed under radically different conditions to those required for alkene and diene hydroborations, typically with much simpler catalysts and no requirement for either ligands or catalyst activation.

The group of Enthaler screened a large number of  $\text{Fe}^0_n(\text{CO})_m$  complexes for the hydroboration of alkynes with HBpin under thermal conditions.<sup>433</sup>  $\text{Fe}^0_2(\text{CO})_9$ , in toluene, at 100 °C for 24 h proved to be most successful conditions, and so the substrate scope of reaction was probed using these (Scheme 4.24). Terminal aryl- and alkyl- alkynes proved to be good substrates for the syn-addition of HBpin, giving the corresponding (*E*)-vinyl-boronate products (18 examples, up to 99% yield, up to 99% (*E*)-selectivity). Disubstituted alkynes were also investigated, but typically gave complex mixtures of products with poor selectivity (6 examples 53-99% conversion).

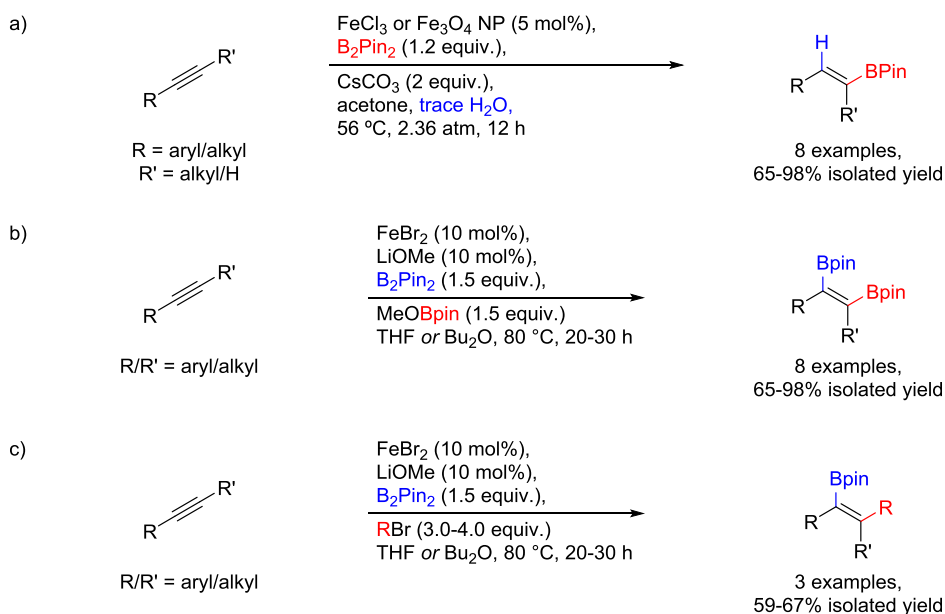


R = H, 18 examples (up to 99% yield and (*E*)-selective)  
R = aryl/alkyl, 6 examples (53-99% conversion, mixture of products)

**Scheme 4.24**  $\text{Fe}^0_2(\text{CO})_9$  catalysed hydroboration of alkynes reported by Enthaler and co-workers.<sup>433</sup>

Rawat and Sreedhar have published an operationally simple protocol for the formal hydroboration of alkynes using either iron(III) chloride or magnetically-recoverable iron oxide ( $\text{Fe}_3\text{O}_4$ ) nano particles and  $\text{B}_2\text{Pin}_2$  as the boron source (Scheme 4.25 a). An inorganic base ( $\text{CsCO}_3$ ) was found to be indispensable. The reaction was performed under air, albeit at elevated temperatures in a sealed vessel, and it was found that traces of water in the solvents was the source of hydrogen. No catalytic cycle was proposed.<sup>434</sup>

Additionally, M. Nakamura has published a formal diboration of alkynes catalysed by  $\text{FeBr}_2$  (8 examples, 65-98% isolated yield, Scheme 4.25 b).<sup>435</sup> Mechanistic investigations by DFT calculation, revealed that the reaction proceeds by a borometallation reaction to generate an alkyl-iron intermediate, which then attacks the electrophilic boron reagent  $\text{MeOBpin}$ . Reaction conditions were also developed where the electrophilic boron reagent was replaced with an electrophilic alkylating agent to give the products of a formal carboboration (3 examples 59-67% isolated yield, Scheme 4.25 c). The use of radical clock alkenes (*vide supra*) as electrophiles revealed that the reaction proceeds through alkyl-radical intermediates.

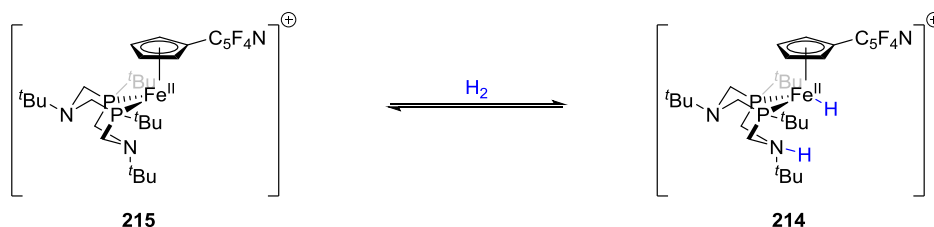


**Scheme 4.25** Formal a) hydroboration, b) diboration and c) carboration of alkynes, catalysed by simple iron salts.<sup>434,435</sup>

#### 4.2.4 NON-INNOCENT LIGANDS IN IRON CATALYSIS

A great deal of the chemistry of iron-catalysis has utilised redox non-innocent ligands in order to modulate and increase catalytic activity (*vide supra*). An alternative strategy is the use of chemically non-innocent ligands to promote cleavage of substrates, as a substitute for M<sup>n</sup>/M<sup>n+2</sup> redox pair, in particular the use of ligands with a non-labile anchoring group, and a labile or semi-labile tethered (or pendent) Lewis base.

This strategy has been exploited by the group of Bullock to perform the heterolytic cleavage of H<sub>2</sub>, generating metal-hydrides and a ligand supported proton.<sup>436</sup> Significantly, this work has allowed the generation and characterisation of the iron-hydride complex **214** from cationic complex **215** and H<sub>2</sub> gas, followed by electro-chemical oxidation (Scheme 4.26).<sup>437</sup> While alkyl-phosphine ligands can be difficult to handle related complexes have been used for alkene hydrogenation (*vide supra*).<sup>198</sup>



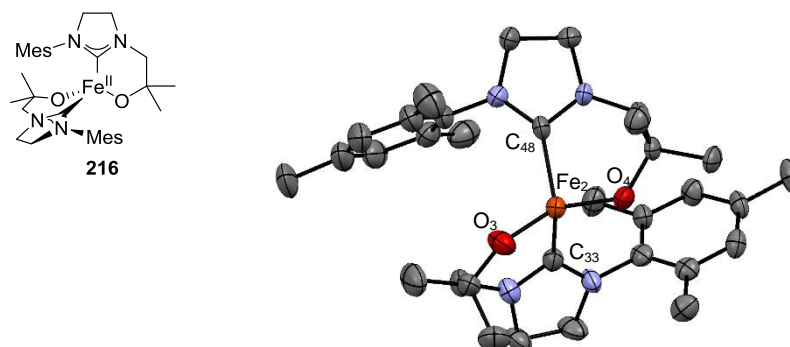
**Scheme 4.26** Heterolytic cleavage of H<sub>2</sub> by complex **215**, a demonstration of ligand assistance for substrate activation.<sup>437</sup>

We therefore required a ligand class with a strong anchoring group, along with a labile or semi-labile tether.<sup>438</sup> This was provided by alkoxy-tethered NHCs, a class of ligand that has not been thoroughly investigated, but which offers a great deal of potential reactivity.<sup>439</sup>

NHCs are persistent singlet carbenes,<sup>440</sup> formed by the deprotonation of air- and moisture stable precursor imidazolium or imidazolinium salts. The resultant carbenes can be air- stable, dependent on the steric bulk of side groups.<sup>440</sup> The lone-pair on NHCs act as neutral Lewis-bases, and therefore they are commonly (but certainly not exclusively) exploited as 2-electron  $\sigma$ -donor ligands, that undergo minimal  $\pi$ -backbonding.<sup>441,442</sup>

A large number of syntheses for NHC precursors exist, many of which are highly modular, which has led to a rapid development in diversity structures and therefore properties of these compounds.<sup>443</sup> Quantifying the properties of NHCs is therefore non-trivial,<sup>442,444</sup> but empirical tuning of the properties of NHC ligands, allows the tuning of the catalytic properties of the derived complexes.

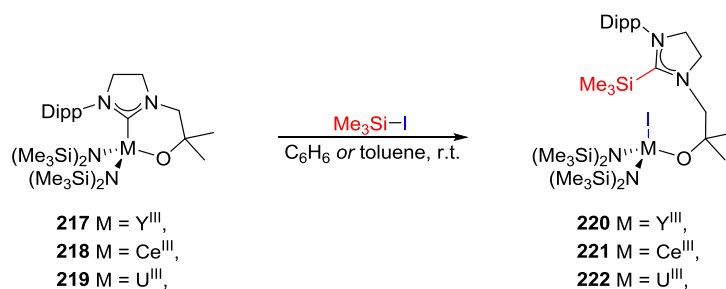
The group of Arnold has reported myriad metal complexes ligated by alkoxy- tethered, NHC ligand as part of a decade-long research project, including, recently, a bis-ligated Fe<sup>II</sup> NHC complex **216**.<sup>445</sup>



**Figure 4.02** Structure of complex **216**, courtesy of A. Fyfe (PhD thesis).<sup>445</sup>

Significantly these complexes include examples of uranium(III), cerium(III) and yttrium(III) complexes **217-219** with two anionic N(SiMe<sub>3</sub>)<sub>2</sub> amide ligands and a single alkoxy-tethered NHC ligand, which on treatment with Me<sub>3</sub>SiI results in heterolytic cleavage of the Si-I bond and the generation of complexes **220-222**.<sup>446</sup> This is an incontrovertible example of ligand assisted substrate activation to give the product of a  $\sigma$ -bond metathesis-type reaction. However, metal-amide complexes tend not to be air- or moisture stable, so catalytic examples using these complexes have not been reported.

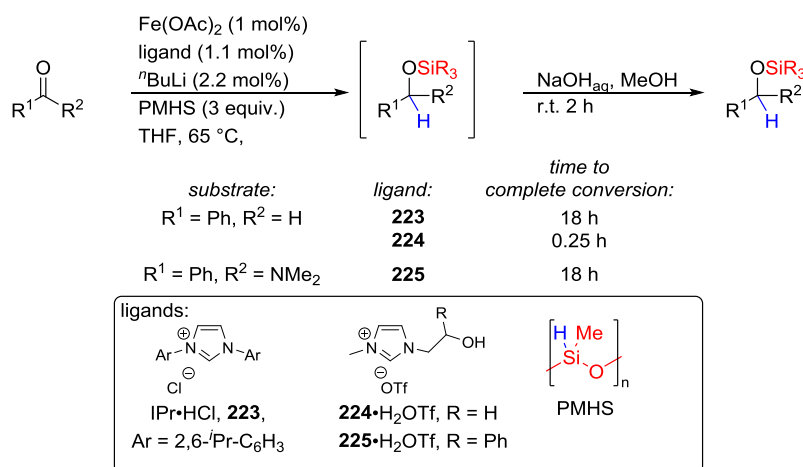




**Scheme 4.27** Alkoxy-tethered NHCs complexes undergo metallocycle ring-opening/iodosilane activation, as reported by Arnold and co-workers.<sup>446</sup>

A large number of iron complexes bearing NHC ligands have been reported and utilised in catalysis, however, only a very small number have been supported by base tethered NHCs, these are detailed below.<sup>447</sup>

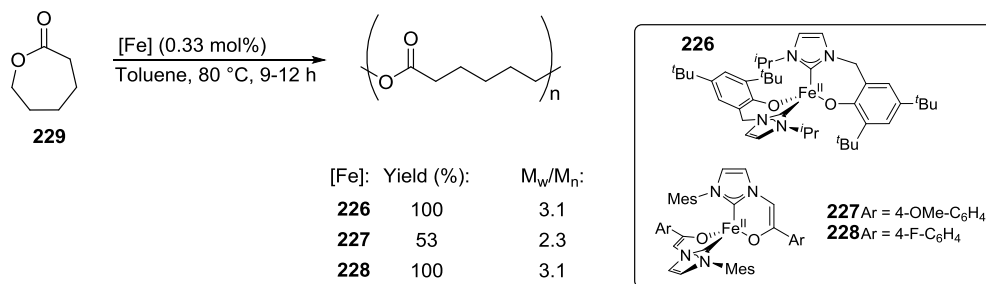
The group of Adolffson have reported reduction by hydrosilylation of carbonyl complexes catalysed by *in situ* formed iron NHC complexes, that were not isolated or characterised, using both conventional IPr **223** ligand,<sup>448</sup> and alkoxy-tethered NHCs **224** and **225** (Scheme 4.28).<sup>448</sup> The researchers observed significant rate enhancement when using the later system, and were able to expand the reaction scope to include amides. Little mechanistic investigation was performed to find the origin of the considerable rate enhancement.<sup>449</sup>



**Scheme 4.28** Adolffson and co-workers' hydrosilylation of carbonyls, rate enhancement by using alkoxy-tethered NHC ligands.

The group of Shen has reported the synthesis and characterisation of iron(II) complex **226** bearing an aryloxy-tethered NHC ligand and complexes **227-228** bearing enolate-tethered ligands.<sup>450,451</sup> These complexes adopt the same distorted tetrahedral structure observed by the Arnold group in complex **216**. Attempts to produce analogous complexes with only one NHC ligand were unsuccessful. The isolated complexes were demonstrated to be active for the ring-

opening polymerisation (ROP) of  $\epsilon$ -caprolactone **229**, albeit with poor control over the dispersity ( $M_w/M_n$  where  $M_w$  is the weight average molecular mass and  $M_n$  the number average molecular mass).



**Scheme 4.29** Shen and co-workers ROP of  $\epsilon$ -caprolactone **229** catalysed by alkoxy- tethered NHC complexes **226-228**.<sup>450</sup>

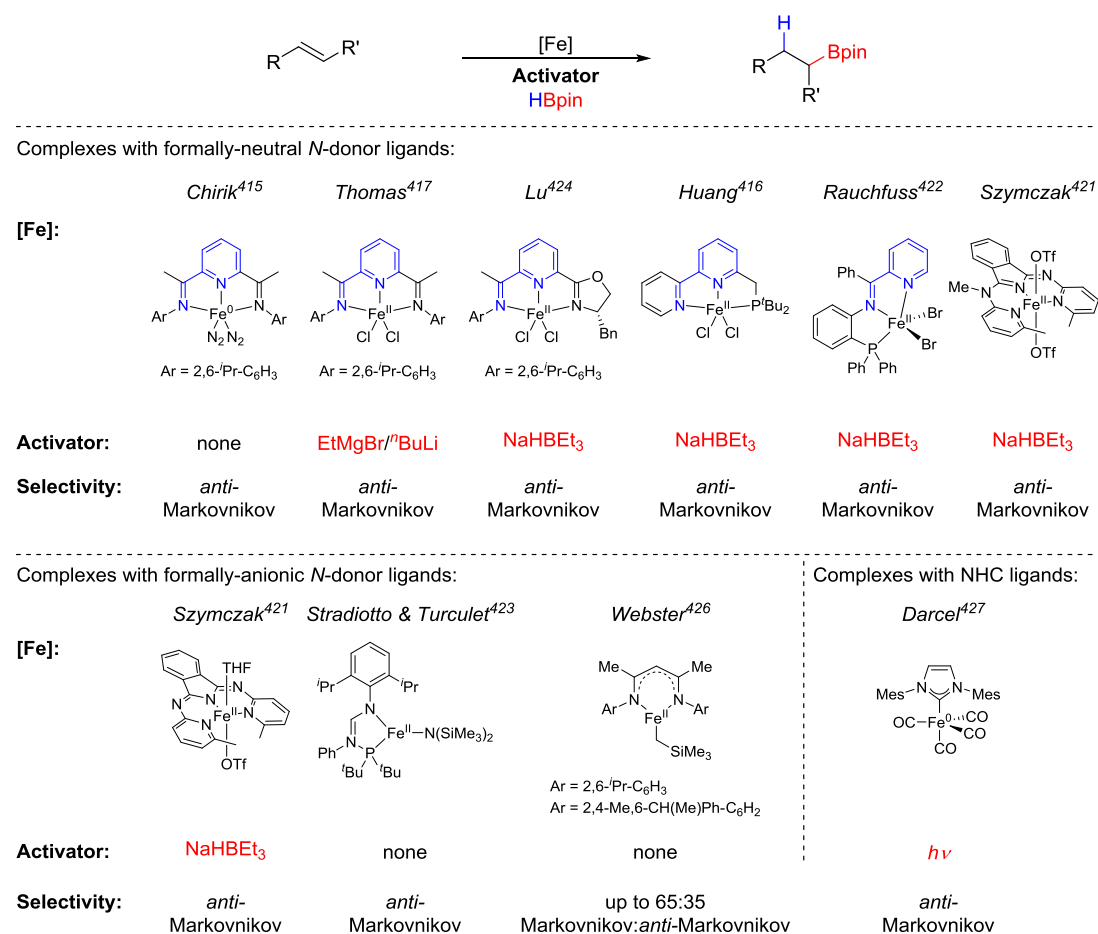
### 4.3 PROJECT AIMS

Precious metal-catalysed alkene hydroboration reactions are a largely ‘mature’ field, in which systems have been developed with high activity and selectivity for most target types.<sup>383,384,401,452,453</sup> Although high chemoselectivity, regioselectivity and enantioselectivity can be achieved using precious-metals, there is still limited precedent for the direct generation of bench-stable pinacol boronic esters by use of pinacol borane (HBpin), and precious metals suffer from inherent toxicity, cost and sustainability concerns.

The use of iron-catalysis for alkene hydroboration has only recently started to be explored. Only a very limited selection of complexes and reagents have been investigated in the existing literature. To date, iron- alkene hydroboration has been achieved using: well-defined low oxidation-state complexes;<sup>415,427</sup> *in situ* activation of ligated metal(II) pre-catalysts using organometallic reagents;<sup>416,417,421–424</sup> and an alkyl-iron complex.<sup>426</sup> These systems (with the work of Darcel being a notable exception) all utilise either neutral *N*-donor ligands or anionic amide donor ligands (Scheme 4.30). In particular, the imino-pyridine motif (highlighted in blue) is extremely prevalent and even where it is not present, extended  $\pi$ -systems are used. The imino-pyridine motif is able to both donate and accept electron density from a metal centre and appears to be critical for highly active iron-based hydroboration catalysts.<sup>214–217,454</sup>

Those examples that do not require *in situ* activation (the work of Chirik, Stradiotto and Turculet, and Webster) are pre-activated complexes that are highly air- and moisture sensitive. The majority of these reported catalytic systems however use air- and moisture stable pre-catalysts activated *in situ* by reductive organometallic species, which makes interpreting the identity and oxidation-state of the catalytically active iron species difficult. Additionally, the

activation with (air- and moisture sensitive) organometallic reagents adds additional operational complexity.



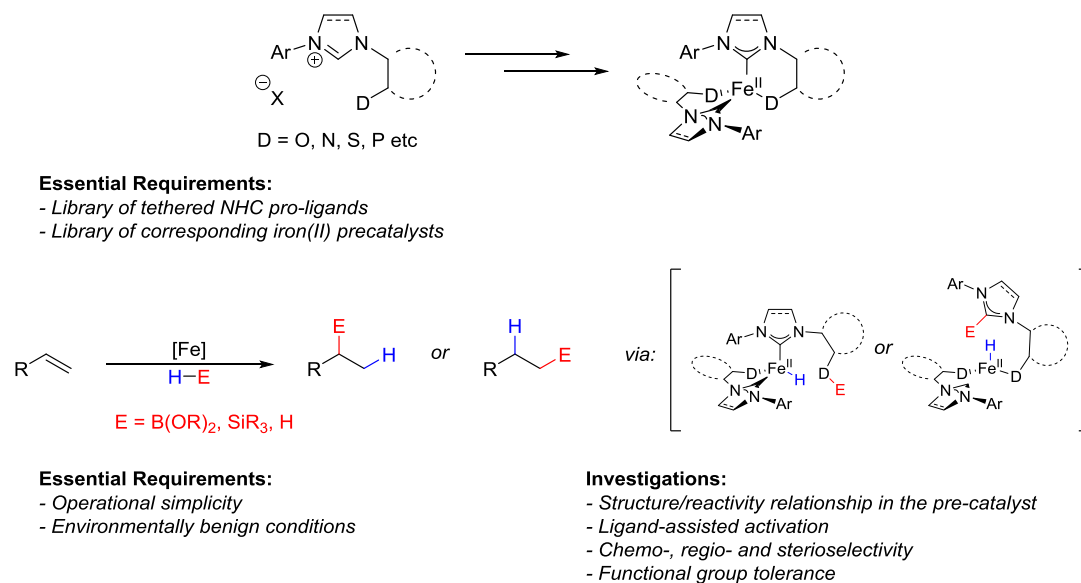
**Scheme 4.30** Overview of the current state-of-the-art in iron-catalysed alkene hydroboration. Highly conserved imino-pyridine motif highlighted in blue.

Conservatism in complex design has led to, in all previously reported cases, hydroboration reactions are either highly *anti*-Markovnikov selective or give a non-synthetically useful mixture of regioisomeric boronic ester products (the highest reported Markovnikov:*anti*-Markovnikov selectivity for styrene is 65:35).<sup>426</sup> Thus, there is a clear need for an earth abundant metal-catalysed hydroboration that proceeds with Markovnikov selectivity.

The aim of this project was to sought to develop a novel iron-catalysed hydrofunctionalisation reaction which would proceed under operationally simple conditions: easily handled reagents and without the need for an external activator. Ideally the both the pre-catalyst and reaction mixtures will be air- and moisture stable. As part of the Thomas groups' continuing research efforts on the development of novel activation modes for earth abundant metal catalysts we postulated that with appropriate design, ligand assistance could be used to enable catalyst activation. Thus, a dual-function ligand would be needed where an anchoring group and

activating group are incorporated into a single structure. *N*-Heterocyclic carbenes (NHCs) have been shown to be effective and versatile ligands in iron catalysis, so could act as our anchoring group.<sup>38–40</sup> Alkoxy-tethered NHC ligands have been proposed to activate silanes for the hydrosilylation of carbonyl derivatives, so may offer an activation mode that could be developed to enable alkene hydroboration using boronic esters.<sup>41,42</sup>

To this end a range of iron(II) complexes with Lewis base-tethered NHC ligands were to be synthesised, of sufficient diversity to provide a useful range of test complexes. This library of complexes was then be screened for hydrofunctionalisation reactivity (Scheme 4.31).



**Scheme 4.31** Project aims: the development of iron(II) complexes with tethered NHC ligands and investigating their activity as hydroboration catalysts.

## 4.4 RESULTS AND DISCUSSION

### 4.4.1 SYNTHESIS OF ALKOXY-TETHERED *N*-HETEROCYCLIC CARBENE IRON(II) COMPLEXES

#### 4.4.1.1 Synthesis of Aryloxy-Tethered Imidazolinium Salts

Initial studies focused on producing imidazolinium salt NHC precursors. These pro-ligands with fully saturated backbones were targeted due to these ligands being unable to undergo ‘normal’ to ‘abnormal’ bonding rearrangements, which iron(II) complexes bearing imidazolium derived NHC ligands have been reported to undergo.<sup>455</sup>

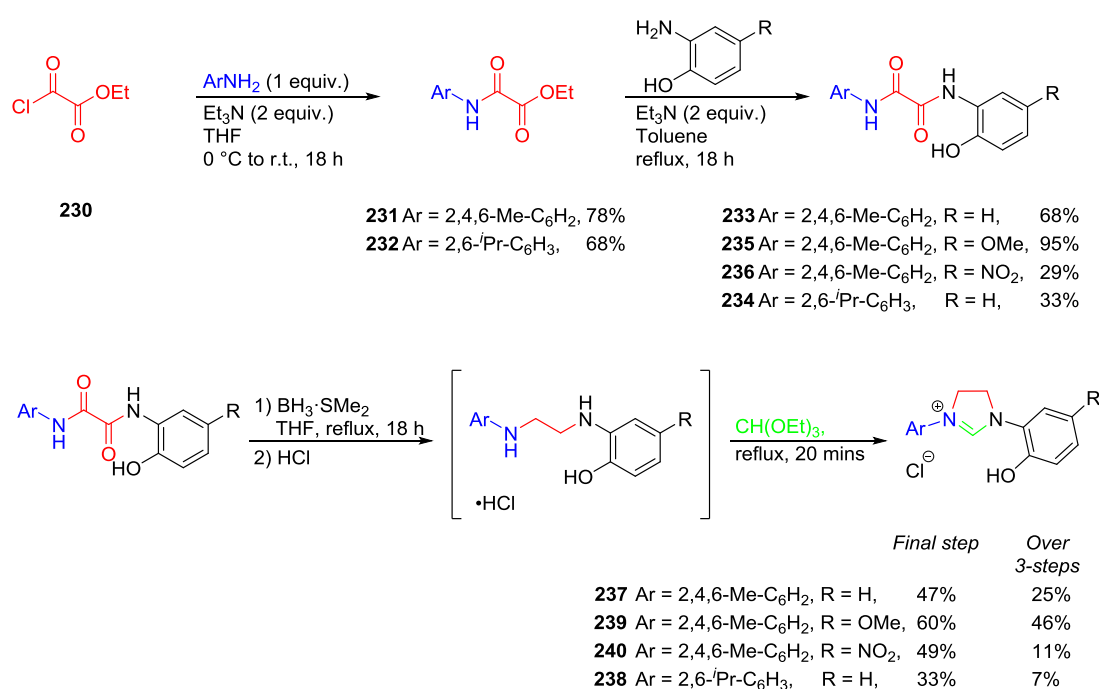
A modular approach to the synthesis of phenoxy-functionalised imidazolinium salts, previously reported by Grubbs and co-workers,<sup>456,457</sup> was used to produce a range of pro-ligands (Scheme 4.32). This synthetic route allows access to unsymmetric NHC precursors from an unsymmetric

ethyl chlorooxoacetate **230** starting material. Variation of steric demand around the NHC was achieved by performing the first amide condensation with either 2,4,6-trimethylaniline or 2,6-diisopropylaniline to give the amides **231** and **232** in excellent yields following purification by recrystallisation.

Systematic variation of the electronic demand around the *O*-functionalised side-arm was achieved by using electronically differentiated aniline derivatives to give unsymmetrical bis-amide intermediates bearing relatively electron-neutral (**233** and **234**), electron-rich (**235**) and electron-deficient (**236**) functional groups. These intermediates could also be purified on multi-gram scale by recrystallisation from toluene.

These intermediates were converted to the corresponding imidazolinium salts by, firstly reduction with  $\text{BH}_3 \cdot \text{SMe}_2$  complex to give bis-amines, which were not isolated but carried forwards in a one-pot protocol to a ring-closing reaction with triethoxy orthoformate to give NHC precursors **237-240**, which could be isolated in high purity following a simple filtration.

The unsymmetric, aryloxy- functionalised NHC precursors were produced in up to 40% over the 3-step process, and used without further purification.



**Scheme 4.32** Synthesis of unsymmetric aryloxy- functionalised imidazolinium salts **237-240**. Isolated yields reported.

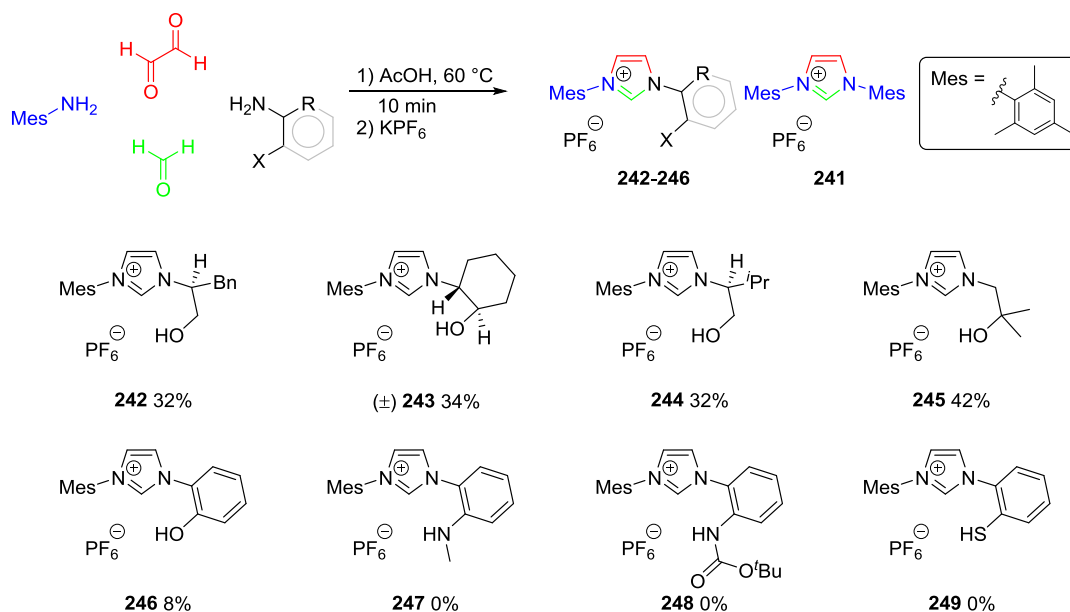
A number of other unsymmetrical pro-ligands were also synthesised, however they were not obtained with sufficient yield and/or purity to carry forwards to complex synthesis.

#### 4.4.1.2 Synthesis of Alkoxy-Tethered Imidazolium Salts

During the synthesis phase of this project, a one-pot method for the synthesis of unsymmetrical imidazolium salts was reported by the group of Mauduit.<sup>458</sup> The reported synthetic procedure was to react glyoxal, formaldehyde and two different amines in aqueous acetic acid at 60 °C for 5 minutes. The reaction generated the mixed unsymmetric NHC precursors as the primary product, along with the two symmetrical side products. The target imidazolium salt could be isolated by recrystallisation. This method was demonstrated to be highly successful for the synthesis of unsymmetrical alkyl-/aryl- substituted imidazolium salts. If this reaction could be expanded to produce aryloxy- and alkoxy- substituted NHC precursors, it would allow access to a wide variety of proligands by a simple and rapid synthesis.

Initial attempts to utilise this method for the synthesis of unsymmetrical, aryloxy- and alkoxy- substituted imidazolium salts were unsuccessful. The reactions produced mixtures of the target unsymmetrical product and the 1,3-bis(2,4,6-trimethylphenyl)-imidazolium (IMes) salt **241**, along with a uncharacterisable brown tar. The two well-defined products could not be readily isolated from the tar.

A later publication by the same group resolved this problem by performing a salt-metathesis reaction to provide the imidazolium hexafluorophosphate salt.<sup>459</sup> These could then be separated from both the IMes side product and the tar by flash column chromatography. Following this protocol, a range of alkoxy- **242-245** and aryloxy- substituted **246** imidazolium salts were synthesised (Scheme 4.33). Attempts to use this synthesis for the production of amine, carbamate and thiol substituted imidazolium salts **247-249** were unsuccessful, giving only brown tars with none of the target products observable by <sup>1</sup>H NMR spectroscopy.

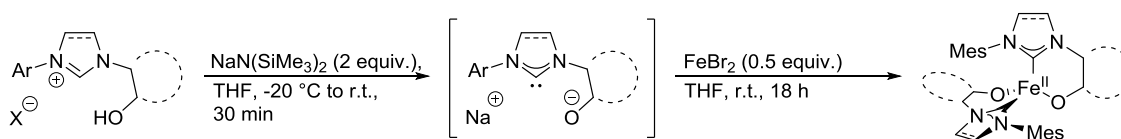


**Scheme 4.33** One-pot multicomponent reactions to give unsymmetrical alkoxy- and aryloxy-functionalised imidazolium salts.

#### 4.4.1.3 Synthesis of Novel Iron(II) NHC Complexes

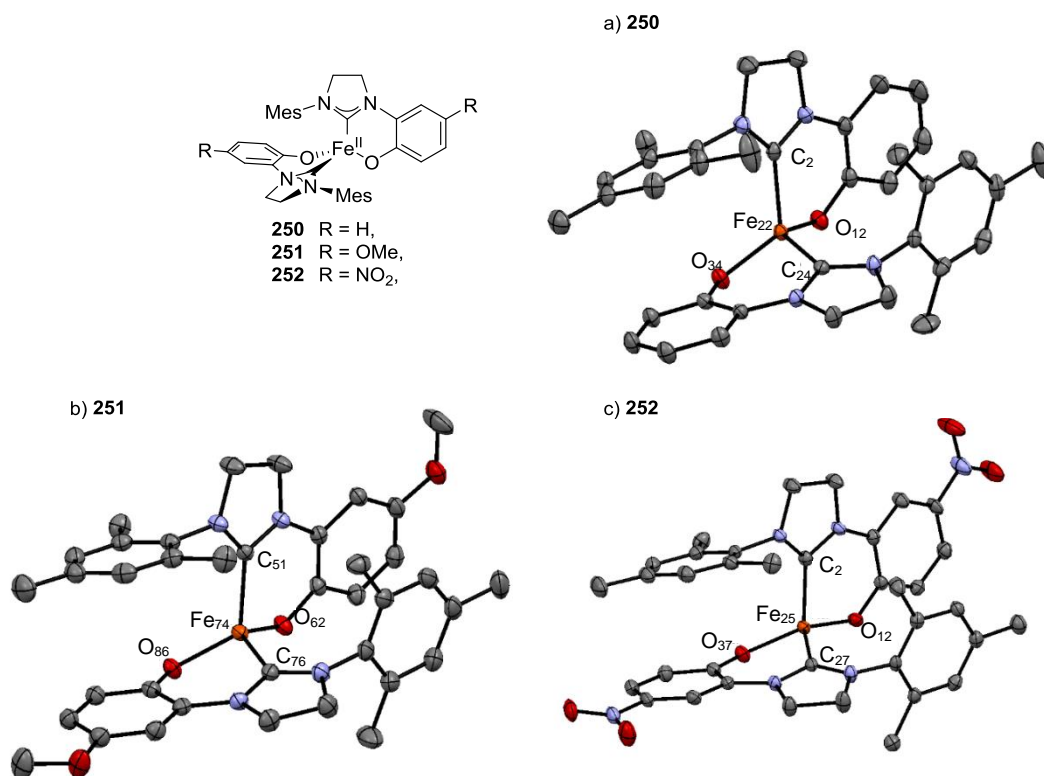
These two synthetic routes produced a wide range of electronically- and sterically diverse imidazolium and imidazolium salts NHC precursors. Arguable too many pro-ligands, since within the time-frame of the project it was not possible to synthesise and characterise iron(II) complexes derived from all the synthesised pro-ligands.

Pro-ligands **237**, **239**, **240** were doubly deprotonated with NaN(SiMe<sub>3</sub>)<sub>2</sub> (2 equivalents) to give the free ligands, which were not isolated, but immediately reacted on with FeBr<sub>2</sub> (0.5 equivalents).<sup>450,451</sup> This reaction is thermodynamically driven by the formation of one equivalent of NaCl and one of NaBr as byproducts.



**Scheme 4.34** Deprotonation of NHC ligand precursors with NaN(SiMe<sub>3</sub>)<sub>2</sub> to give the corresponding ligand followed by coordination to iron(II).

The reactions between aryloxy- functionalised, imidazolinium-derived, NHC ligands and  $\text{FeBr}_2$  resulted in paramagnetic, air- and moisture sensitive solids **250-252**. These solids were successfully recrystallised by slow evaporation of THF, giving crystals suitable for X-ray spectroscopic analysis. Mass-spectroscopy and single-crystal X-ray analysis revealed that these products were bis-ligated complexes with a distorted tetrahedral structure, similar to those previously reported (Figure 4.03).<sup>445,450,451</sup>



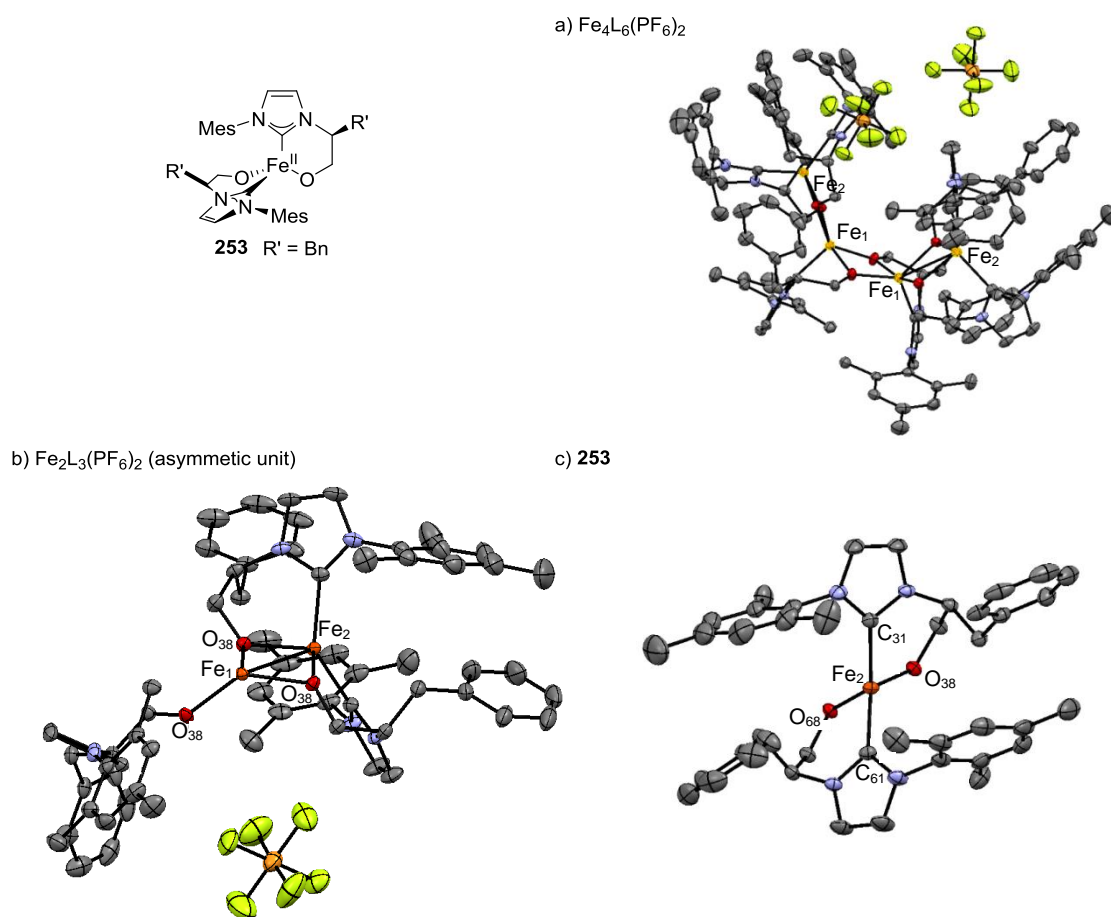
**Figure 4.03** Molecular structure of a) complex **250** b) complex **251** and c) complex **252**. 50% probability of ellipsoids; Hydrogen atoms and solvent molecules omitted for clarity; Grey = C, Blue = N, Red = O, Orange = Fe. CCDC 1487368-1487370 contains the supplementary crystallographic data for these structures. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

The effective magnetic moment ( $\mu_{\text{eff}}$ ) of complex **250** was measured by the Evans NMR spectroscopy method, against a  $\text{Si}(\text{SiMe}_3)_4$  internal standard.<sup>460–462</sup> The effective magnetic moment  $\mu_{\text{eff}} = 5.82 \mu_{\text{B}}$ , which corresponds to high-spin iron(II) with 4 unpaired electrons, corresponding to the charge balancing on the crystal structure and confirmed that no redox events were occurring during complex formation.

No examples of complexes with alkoxy- functionalised imidazolium-derived ligands were successfully crystallised or otherwise isolated.



The products of the reactions between alkoxy- functionalised ligands **242** and **244** were more challenging to isolate and characterise. Mass spectroscopy confirmed the formation of a bis-ligated iron complex **253**, however purification proved challenging. The NaPF<sub>6</sub> byproduct proved to be highly soluble, and could not be removed by filtration from THF. Attempts to remove the byproduct by dissolving the crude products in toluene (in which NaPF<sub>6</sub> is insoluble) and filtering the resulting suspension resulting in decomposition of complexes. Multiple attempts were made to develop conditions for purification by crystallisation, however no success was achieved. Crystals were obtained (after several weeks) by slow evaporation of THF and benzene, however these were of the form Fe<sub>4</sub>L<sub>6</sub>(PF<sub>6</sub>)<sub>2</sub> following disproportionation of the FeL<sub>2</sub> complex with NaPF<sub>6</sub> (Figure 4.04). These crystals did at least provide confirmation that the alkoxy-functionalised complexes also adopt the same distorted tetrahedral geometry as complexes **250-252**.



**Figure 4.04** Molecular structure of complex **253**. a)  $\text{Fe}_4\text{L}_6(\text{PF}_6)_2$ , b) asymmetric unit,  $\text{Fe}_2\text{L}_3(\text{PF}_6)_2$  c) tetrahedral unit,  $\text{FeL}_2$ . 50% probability of ellipsoids; Hydrogen atoms and solvent molecules omitted for clarity; Grey = C, Blue = N, Red = O, Orange = Fe. CCDC 1487371 contains the supplementary crystallographic data for these structures. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

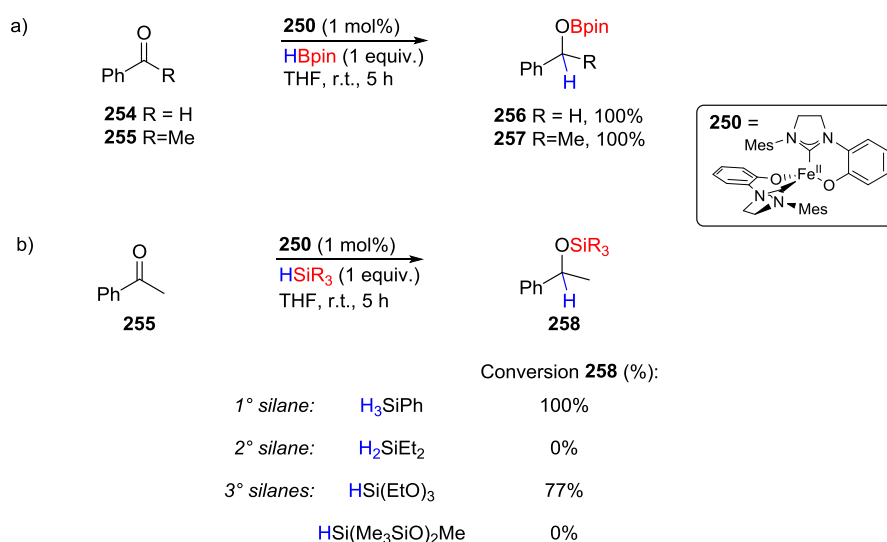
In conclusion four bis-ligated, tetrahedral iron(II) NHC complexes have been synthesised and characterised: three complexes with aryloxy- functionalised ligand; and one with an alkoxy-functionalised ligand.

It is worth noting at this point, that even with ligand synthesis, complex **253** (for example) was prepared in 2-steps and at considerably less cost than even commercially available Wilkinson's catalyst. (Costs for complex **253** break down as follows: ligand approximately £10/mmol; iron(II) bromide approximately £1/mmol;  $\text{Na}(\text{SiMe}_3)_2$  (1.0 M in THF) approximately £0.50/mmol; complex synthesis (85% yield) approximately £14/mmol. Cost for Wilkinson's catalyst: approximately £70/mmol).

#### 4.4.2 PRELIMINARY ASSESSMENT OF CATALYTIC ACTIVITY

These complexes were next screened for catalytic activity in alkene hydrofunctionalisation reactions. Aryloxy-tethered iron(II) complex **250** had been synthesised in the greatest quantities and so was used for this initial screening work.

The reduction of carbonyl compounds, benzaldehyde **254** and acetophenone **255**, was used to initially assess the catalytic hydrofunctionalisation activity of complex **250**. Complex **250** was able to rapidly catalyse the hydroboration of both benzaldehyde **254** and acetophenone **255** using HBpin with quantitative conversion (Scheme 4.35 a). Complex **250** was also active for the reductive hydrosilylation of **255**, however the results in this case were complicated by the identity of the silane (Scheme 4.35 b). Phenylsilane and triethoxysilane gave conversions to the silyl-protected 1-phenylethanol derivative **258** of 100% and 77% respectively, whereas diethylsilane and 1,1,1,3,5,5,5-heptamethyltrisiloxane gave no conversion to product. This is in accordance with previously reported work of hydrosilylation, in which the identity of the silane can have a dramatic effect on the reactivity observed.<sup>419</sup>

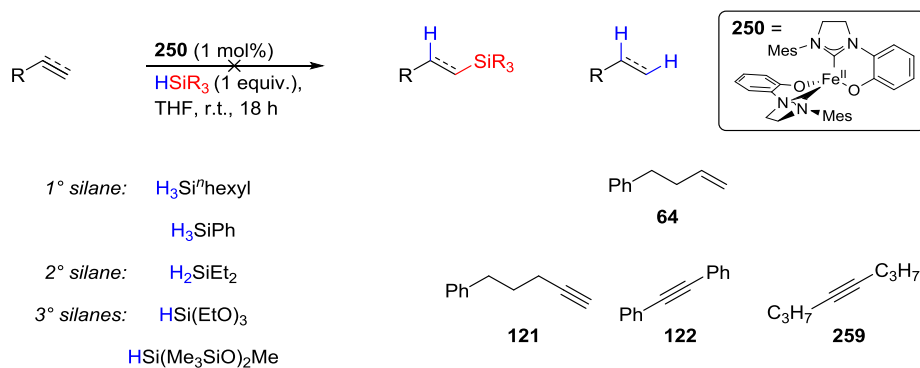


**Scheme 4.35** Complex **250** catalysed reduction of benzaldehyde **254** and acetophenone **255** by a) hydroboration with HBpin and b) hydrosilylation with various silanes.

These results were promising, indicating that the complexes could be catalytically active for hydrofunctionalisation reactions. However, iron-catalysed reduction of carbonyl compounds are well-known with iron catalysts acting as Lewis acids. Therefore the research moved on to the more challenging and relevant hydrofunctionalisation of alkenes.

Studies towards the development of conditions for the complex **250** catalysed hydroboration of alkenes are detailed in the following sections.

Complex **250** was screened for activity in the hydrosilylation of 4-phenyl-1-butene **64**, using a range of primary, secondary and tertiary silane reagents (Scheme 4.36). In all cases, only alkene isomerisation and hydrogenation products, **65** and **66** were identified. Additionally, complex **250** was screened for alkyne hydrogenation with several alkynes **121**, **122**, **259**. In these cases, no reaction was observed.



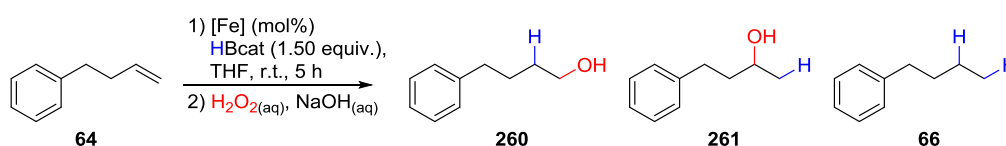
**Scheme 4.36** No conditions were found that were suitable for the **250** catalysed hydrosilylation of alkene **64** or alkynes **121**, **122**, **259**.

### 4.4.3 DEVELOPMENT OF IRON(II)-CATALYSED HYDROBORATIONS USING CATECHOLBORANE

#### 4.4.3.1 Methodology Development

Aryloxy- tethered complexes **250-252** were screened for the hydroboration of 4-phenyl-1-butene **64** with HBcat (1.50 equiv.) in THF (Table 4.4-1, Entries 3, 5-8). Using 5 mol% **250** the *anti*-Markovnikov hydroboration product was obtained, following oxidation to give the linear alcohol, in 87% yield. Interestingly, variation of the electronic character of the phenoxy substituent on the catalyst, by using complexes **251** and **252** led to diminished hydroboration yields (Entries 5,6). Alkoxy-tethered complex **253** was considerably less active under these conditions (Entry 8).

**Table 4.4-1 Screen of complexes 250-252 for the hydroboration of 4-phenyl-1-butene with HBcat<sup>a</sup>**

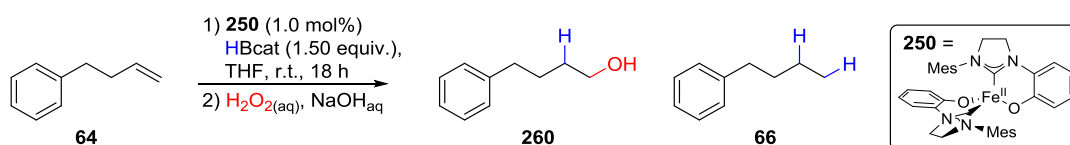


Entry	Catalyst (mol%)	Starting material <b>64</b>	Yield (%) <sup>b</sup>		
			Linear alcohol <b>260</b>	Branched alcohols <b>261</b>	Hydrogenation <b>66</b>
1	none	68	25	-	7
2	<b>250</b> (1)	19	70	6	4
3	<b>250</b> (5)	7	81	8	4
4	<b>250</b> (10)	-	87	10	3
5	<b>251</b> (5)	16	63	8	13
6	<b>252</b> (5)	49	40	5	5
7 <sup>c</sup>	<b>253</b> (5)	16	30	-	8

<sup>a</sup>Conditions: HBcat (1.5 equiv.) was added in a single portion to a solution of [Fe] (2.5 to 10.0 mol%) and 4-phenyl-1-butene **64** (1 equiv.) in THF (0.5 M), r.t., 18 h. Then an aqueous H<sub>2</sub>O<sub>2</sub>/NaOH solution was added in a single portion, 0 °C, 0.5 h. <sup>b</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. <sup>c</sup>Polymerisation observed.

A screen of solvents for the linear hydroboration of 4-phenyl-1-butene **64** with HBcat was performed (Table 4.4-2). Except where otherwise mentioned, all solvents were either obtained from a solvent purification system or purchased in an anhydrous and degassed condition. No solvent was found to outperform anhydrous THF under these conditions (Table 4.4-2, Entry 1). Non-purified reagent grade THF demonstrated considerably diminished yields (Entry 2), demonstrating that the reaction mixture generated is sensitive either to air- and/or moisture or to the stabilisers and impurities present in commercially available THF.

**Table 4.4-2 Screen of solvents for linear hydroboration of 4-phenyl-1-butene **64** with HBcat catalysed by complex **250**<sup>a</sup>**



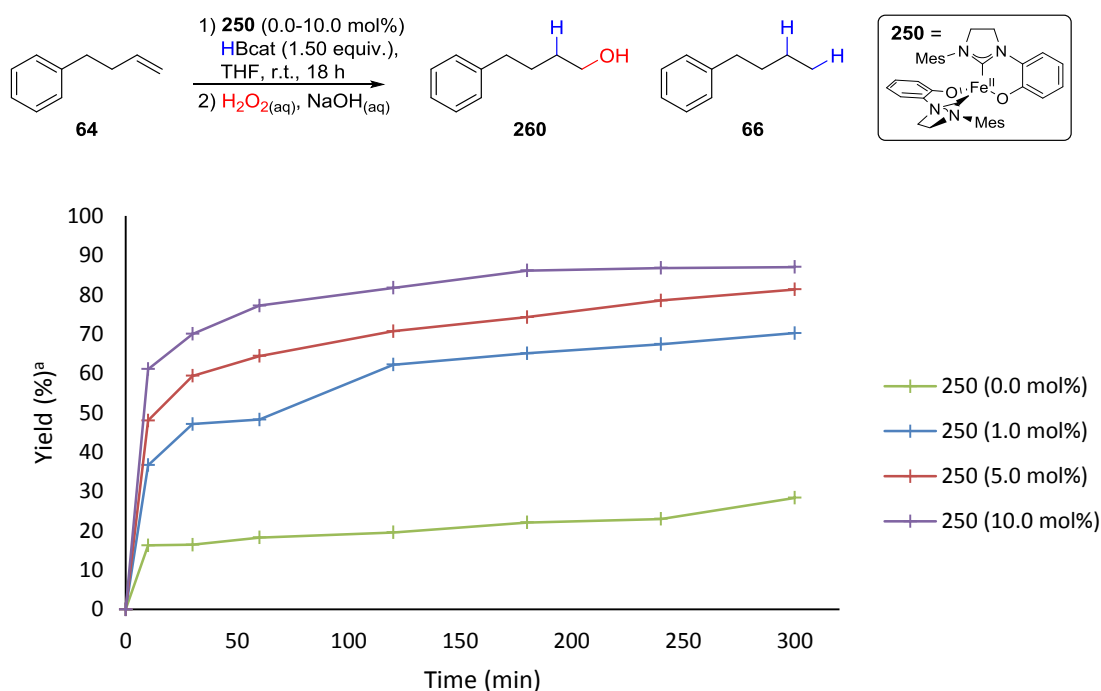
Entry	Solvent	Starting material	Yield (%) <sup>b</sup>	
		<b>64</b>	Linear alcohol <b>260</b>	Hydrogenation <b>66</b>
1	THF	18	<b>70</b>	4
2	THF <sup>c</sup>	27	<b>58</b>	10
3	Et <sub>2</sub> O	63	<b>29</b>	9
4	CH <sub>2</sub> Cl <sub>2</sub>	59	<b>31</b>	10
5	MeCN	4	<b>79</b>	17
7	Toluene	80	<b>20</b>	-
8	MeOH	100	-	-
9	OC(OMe) <sub>2</sub>	41	<b>50</b>	10
10	<sup>t</sup> BuOMe	61	<b>31</b>	8
11	2-MeTHF	39	<b>36</b>	21

<sup>a</sup>Conditions: HBcat (1.5 equiv.) was added in a single portion to a solution of **250** (10 mol%) and 4-phenyl-1-butene **64** (1 equiv.) in solvent (0.5 M), r.t., 18 h. Then an aqueous H<sub>2</sub>O<sub>2</sub>/NaOH solution was added in a single portion, 0 °C, 0.5 h. <sup>b</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard. <sup>c</sup>Reagent-grade THF not dried or degassed.

In order to gain greater insight into the hydroboration reaction, a number of reaction monitoring experiments were performed.

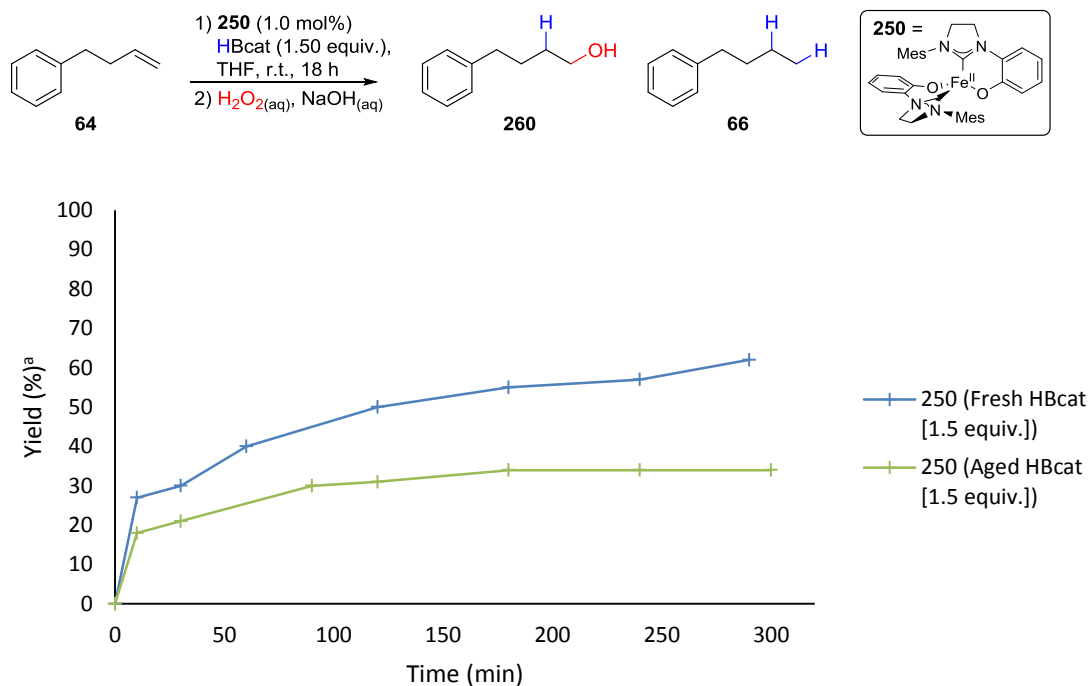
The hydroboration of 4-phenyl-1-butene **64** was performed with HBcat in the presence of complex **250** (0-10 mol%) and monitored by the removal of aliquots from reaction mixture at predetermined time points (Figure 4.05). The aliquots were oxidised with aqueous H<sub>2</sub>O<sub>2</sub>, then diluted with CDCl<sub>3</sub> and analysed by <sup>1</sup>H NMR spectroscopy. The starting material and product peaks can be readily compared to those of the 1,3,5-trimethoxybenzene internal standard to give reaction profiles.

The background reaction with HBcat (0 mol% **250**),<sup>377,378</sup> occurs very rapidly to give ~15% of the hydroboration product before the conversion plateaus. This reactivity can be attributed to residual BH<sub>3</sub> in the HBcat. The products of alkene hydroboration with these two reagents cannot be distinguished in this system due to both being oxidised to the same alcohol **260**. Complex **250** at 1, 5 and 10 mol% loading resulted in extremely rapid conversion in the early part of the reaction, (ca. 10 mins), before a second phase of reaction in which slower hydroboration occurs. 5 and 10 mol% loading of complex **250** on ca. 80% yield, as observed above (Table 4.4-1).



**Figure 4.05** Reaction monitoring of the linear hydroboration of 4-phenyl-1-butene **64** with HBcat, catalysed by complex **250**: variation in complex **250** loading. <sup>a</sup>Yields calculated by <sup>1</sup>H NMR relative to 1,3,5-trimethoxybenzene internal standard. See SI for example of NMR spectra stacks and assignment.

It was found that the reaction only proceeded to a good yield using freshly distilled HBcat. Performing the reaction using HBcat that had been distilled, then aged under an inert atmosphere at  $\sim 5^\circ\text{C}$  for *ca.* 24 h, resulted in a considerable decrease in yield (Figure 4.06). It is known that HBcat undergoes multiple decomposition pathways, even when stored at reduced temperatures, under an inert atmosphere.<sup>380</sup> These results suggest that one (or more) of the decomposition products inhibits the alkene hydroboration reaction.



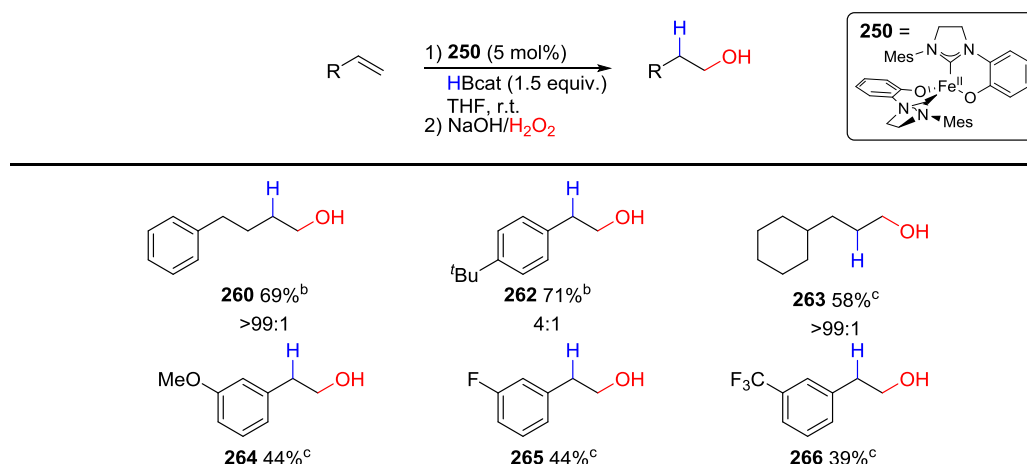
**Figure 4.06** Reaction monitoring of the linear hydroboration of 4-phenyl-1-butene **64** with HBcat, catalysed by complex **250**: effect of allowing HBcat to age prior to use. <sup>a</sup>Yields calculated by  $^1\text{H}$  NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard.

#### 4.4.3.2 Substrate scope

The substrate scope of the hydroboration to give primary alkylboronic esters was investigated with aryloxy-tethered NHC catalyst **250** (5 mol%), HBcat (1.5 equivalents) and various alkenes (Table 4.4-3). Successful catalysis was achieved for terminal alkyl- and aryl- alkenes to give the primary alcohol products **260**, **262-266**, following oxidation with basic hydrogen peroxide. In addition to alkyl-alkenes **260** and **263**, styrene derivatives bearing both electron-withdrawing and -donating arene substituents gave the primary alcohol products in roughly equal yields, albeit decreased from that obtained with alkyl-substituted alkenes.



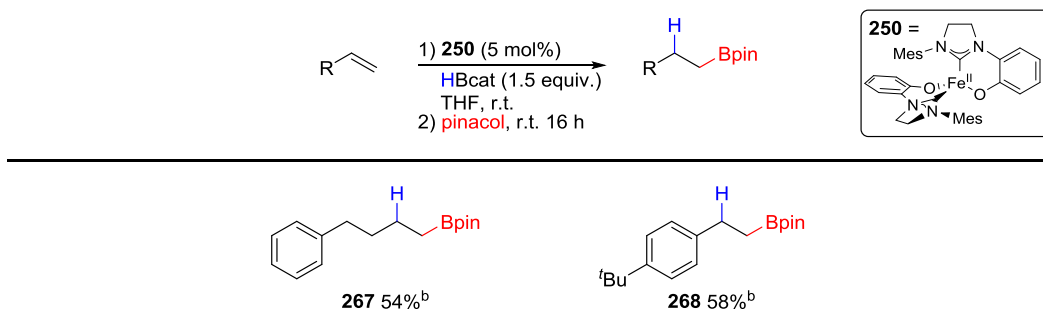
**Table 4.4-3 250 Catalysed, anti-Markovnikov selective hydroboration of alkenes, followed by oxidation<sup>a</sup>**



<sup>a</sup>Conditions: HBcat (1.5 equiv.) was added in a single portion to a solution of **250** (5 mol%) and an alkene (1 equiv.) in THF (0.5 M), r.t., 5 h. Then an aqueous H<sub>2</sub>O<sub>2</sub>/NaOH solution was added in a single portion, 0 °C, 0.5 h. <sup>b</sup>Isolated yields following flash column chromatography, linear:branched ratios calculated from relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Yield measured by <sup>1</sup>H NMR spectroscopy of crude reaction product relative to 1,3,5-trimethoxybenzene internal standard, branched:linear ratios included where available.

Alternatively, the catechol-boronic esters could be transesterified with pinacol to give the thermodynamically stable primary alkyl- boronic ester products **267** and **268** in acceptable yields (Table 4.4-4).<sup>463</sup>

**Table 4.4-4 250 Catalysed, anti-Markovnikov selective hydroboration of alkenes, followed by transesterification<sup>a</sup>**



<sup>a</sup>Conditions: HBcat (1.5 equiv.) was added in a single portion to a solution of **250** (5 mol%) and an alkene (1 equiv.) in THF (0.5 M), r.t., 5 h. Then pinacol (1 equiv.) was added, r.t., 16 h. <sup>b</sup>Isolated yields following flash column chromatography.

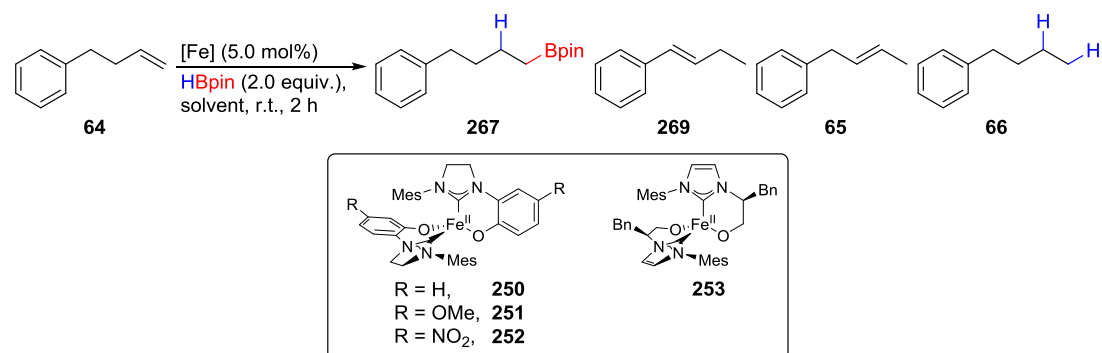
#### 4.4.4 DEVELOPMENT OF IRON(II) CATALYSED HYDROBORATIONS USING PINACOLBORANE

As previously discussed, HBpin has numerous advantages over the more reactive HBcat as a hydroboration reagent: it decomposes less readily and therefore does not typically require distillation prior to use; and the products of hydroboration are typically air- and moisture stable. It was therefore desirable to produce conditions for the direct hydroboration of alkenes using HBpin.

##### 4.4.4.1 Methodology Development

Complexes **250**, **251** and **252** were tested for the hydroboration of 4-phenyl-1-butene **64** using HBpin both in THF and neat. In all cases, only alkene isomerisation products **65** and **269** along with hydrogenation product **66** were observed (Table 4.4-5, Entries 2-6). These alkene isomerisation reactions presumably proceed by hydrometallation of the alkene, followed by  $\beta$ -hydride elimination. This implies the existence of the targeted iron-hydride intermediates. Further screening of conditions was performed to try and exploit these intermediates for alkene hydroboration reactions.

**Table 4.4-5 Screen of complexes 250-253 for the hydroboration of 4-phenyl-1-butene with HBpin<sup>a</sup>**



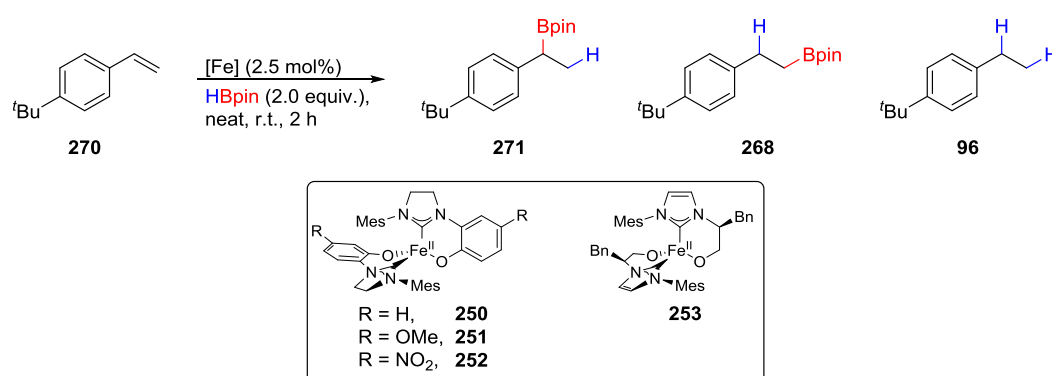
Entry	[Fe] (mol%)	Solvent	Starting material <b>64</b>	Linear hydroboration <b>267</b>	Yields (%) <sup>b</sup> Styrenyl- alkene <b>269</b>	Allyl- alkene <b>65</b>	Hydrogenation <b>66</b>
1	FeBr <sub>2</sub> (5.0)	THF	51	-	-	2	31
2	<b>250</b> (1.0)	THF	15	-	4	49	15
3	<b>251</b> (2.5)	neat	-	-	6	82	11
4	<b>251</b> (2.5)	THF	-	-	20	65	15
5	<b>253</b> (2.5)	THF	-	-	38	44	15
6	<b>253</b> (2.5)	neat	-	<b>3</b>	38	43	15

<sup>a</sup>Conditions: HBpin (2.0 equiv.) was added in a single portion to a solution of [Fe] (1.0 to 5.0 mol%) and 4-phenyl-1-butene **64** (1 equiv.) in THF (0.5 M), r.t., 2 h. <sup>b</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard.

Complexes **250** and **253** were also screened for the hydroboration of 4-*tert*-butylstyrene **96** with HBpin, in a wide range of solvents (see Chapter 5.14 for further details). No solvents were found that were able to support the reaction.

However it was found that by performing the hydroboration of 4-*tert*-butylstyrene **270** with HBpin in the absence of solvent, mixtures of the secondary (**271**) and primary (**268**) alkylboronic ester products could be obtained (Table 4.4-6, Entries 1-5). Significantly, and to the best of the authors' knowledge, this is the first example of a Markovnikov (branched) selective iron-catalysed hydroboration. Complexes **250** and **253** gave the best yields of the branched hydroboration product **271** (Entries 2 and 5) and so were taken forwards for optimisation.

**Table 4.4-6 Screen of complexes 250-253 for the hydroboration of 4-*tert*-butylstyrene with HBpin<sup>a</sup>**



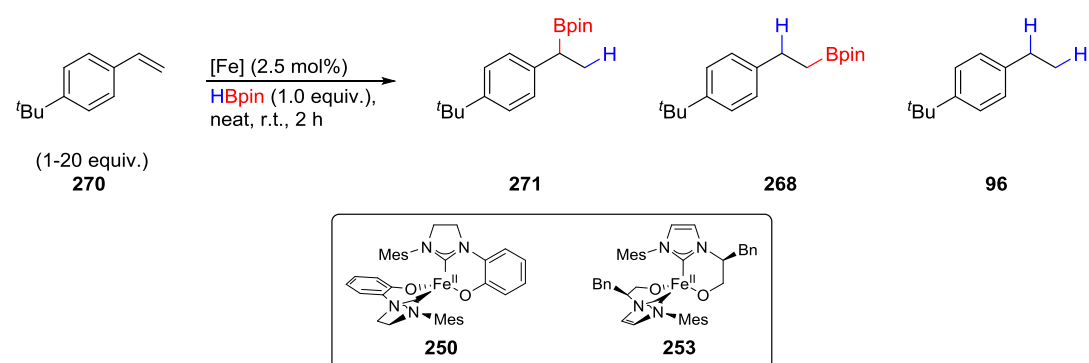
Entry	[Fe] (mol%)	Yield (%) <sup>b</sup>			
		Starting material <b>270</b>	Branched hydroboration <b>271</b>	Linear hydroboration <b>268</b>	Hydrogenation <b>96</b>
1	FeBr <sub>2</sub> (2.5)	54	-	-	20
2	<b>250</b> (2.5)	10	<b>26</b>	5	51
3	<b>251</b> (2.5)	1	<b>16</b>	5	71
4	<b>252</b> (2.5)	6	<b>10</b>	6	54
5	<b>253</b> (2.5)	3	<b>25</b>	3	65

<sup>a</sup>Conditions: HBpin (2.0 equiv.) was added in a single portion to a solution of [Fe] (2.5 mol%) in 4-*tert*-butylstyrene **270** (1 equiv.), r.t., 2 h. <sup>b</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard.

Yields of the secondary boronic ester **271** could be increased for aryloxy-tethered complex **250**, but only by performing the reactions in an excess of the styrene derivative. Increasing the loading of 4-*tert*-butylstyrene **270** to 5 or 10 equivalents gave 67% of the branched hydroboration product **271** (Table 4.4-7, Entry 2, 3). Further increase of **270** to 20 equivalents resulted in a decrease in yield (Entry 4). Only minimal increases in yield from 37% to 45% was

observed on increasing **270** loading when using alkoxy-tethered complex **250** (Entries 5-7).

**Table 4.4-7 Effect of alkene equivalency in the hydroboration of 4-*tert*-butylstyrene with HBpin.<sup>a</sup>**

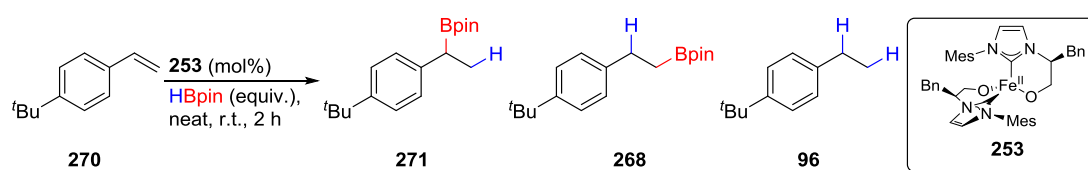


Entry	[Fe] (mol%, M)	270 (equiv.)	Yield (%) <sup>b</sup>			
			Starting material 270	Branched hydroboration 271	Linear hydroboration 268	Hydrogenation 96
1	<b>250</b> (2.5, 0.07)	1	51	<b>19</b>	2	31
2	<b>250</b> (2.5, 0.02)	5	360	<b>67</b>	2	15
3	<b>250</b> (2.5, 0.01)	10	883	<b>67</b>	2	30
4	<b>250</b> (2.5, 0.007)	20	1918	<b>27</b>	2	80
5	<b>253</b> (2.5, 0.07)	1	36	<b>37</b>	6	18
6	<b>253</b> (2.5, 0.02)	5	384	<b>39</b>	3	31
7	<b>253</b> (2.5, 0.01)	10	439 <sup>c</sup>	<b>45</b>	4	41

<sup>a</sup>Conditions: HBpin (2.0 equiv.) was added in a single portion to a solution of [Fe] (2.5 mol%) and 4-*tert*-butylstyrene **270** (1-20 equiv.), r.t., 2 h. <sup>b</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene internal standard, and reported relative to the limiting reagent (HBpin **174**). <sup>c</sup>Polymerisation observed.

A significant breakthrough was found when the order of addition was investigated: adding HBpin to complex **253** prior to addition of 4-*tert*-butylstyrene **270** led to increased yield. The loading of HBpin and alkoxy-tethered complex **253** was investigated under these new conditions (Table 4.4-8). One equivalent of HBpin gave the conversion to the branched hydroboration product **271** of 47% (Table 4.4-8, Entry 1), increasing this to 1.25 or 1.5 equivalents led to 66% and 72% conversion respectively (Entries 2 and 3). However further increasing HBpin loading led to decreased conversion (Entry 4). Variation in the loading of, complex **253** gave no significant increases in yield (Entries 5-8).

**Table 4.4-8 Optimisation of conditions for the 253-catalysed hydroboration of 4-*tert*-butylstyrene.<sup>a</sup>**

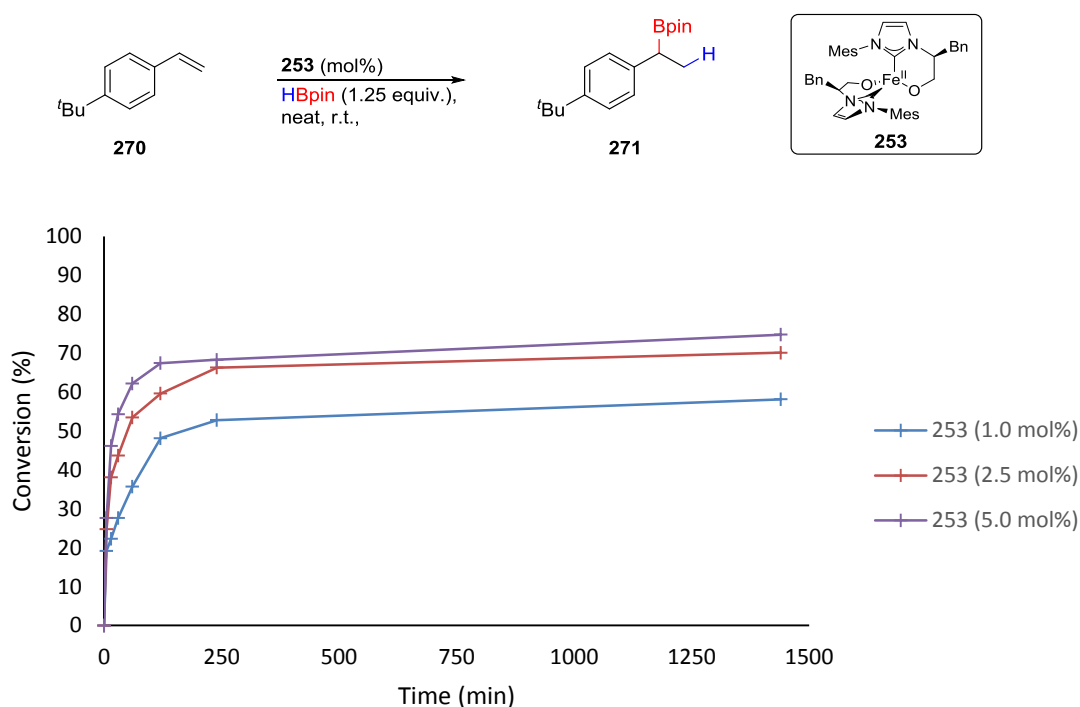


Entry	[Fe] (mol%)	HBpin (equiv.)	T (h)	Conversion (%) <sup>b</sup>			
				Starting material <b>270</b>	Branched hydroboration <b>271</b>	Linear hydroboration <b>268</b>	Hydrogenation <b>96</b>
1	<b>253</b> (2.5)	1.0	3	42	<b>47</b>	5	6
2	<b>253</b> (2.5)	1.25	3	14	<b>66</b>	8	12
3	<b>253</b> (2.5)	1.5	3	11	<b>72</b>	8	9
4	<b>253</b> (2.5)	2.0	3	36	<b>53</b>	6	5
5	<b>253</b> (0.5)	1.25	4	46	<b>31</b>	3	19
6	<b>253</b> (1.0)	1.25	4	23	<b>58</b>	6	13
7	<b>253</b> (5.0)	1.25	4	9	<b>75</b>	9	8

<sup>a</sup>Conditions: HBpin (1.0-2.0 equiv.) added in a single portion to complex **253** (0.5-5.0 mol%) followed after ~15 s by 4-*tert*-butylstyrene **270** (1 equiv.), neat, r.t., 3-4 h. <sup>b</sup>Conversions calculated by <sup>1</sup>H NMR spectroscopy relative to residual starting material.

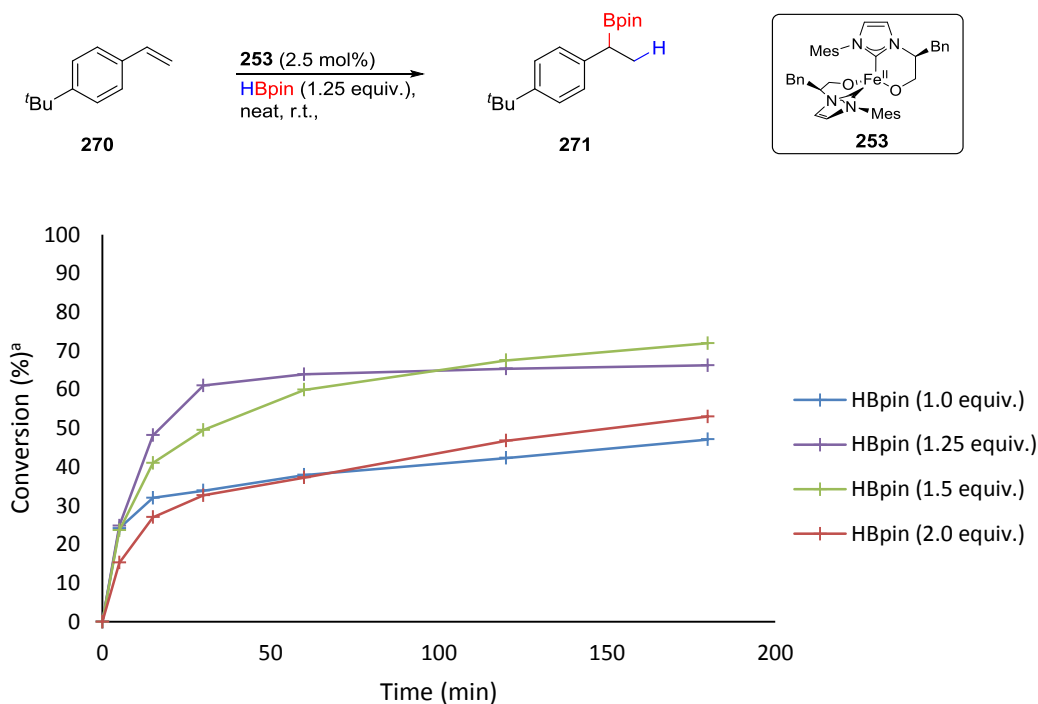
To aid in reaction optimisation, reaction monitoring experiments were also performed on this system, by removing aliquots from a reaction mixture, diluting them with CDCl<sub>3</sub> and analysing them by <sup>1</sup>H and/or <sup>11</sup>B NMR spectroscopy. In this case, the relative integrals of starting material and product peaks was used to calculate conversions, isolation experiments (*vide infra*) demonstrated that these conversions are an accurate representation of the reaction yields.

<sup>1</sup>H NMR spectroscopy was used to monitor the effect of variation in loading of complex **253** from 1.0 mol% to 5.0 mol% (Figure 4.07). The reaction monitoring demonstrated that the reactions typically proceeded to near completion in approximately 1 hour, before plateauing. As noted above, 2.5 mol% and 5 mol% of complex **253** gave very similar yields of the branched hydroboration product at completion, considerably higher than for 1 mol% **253**.



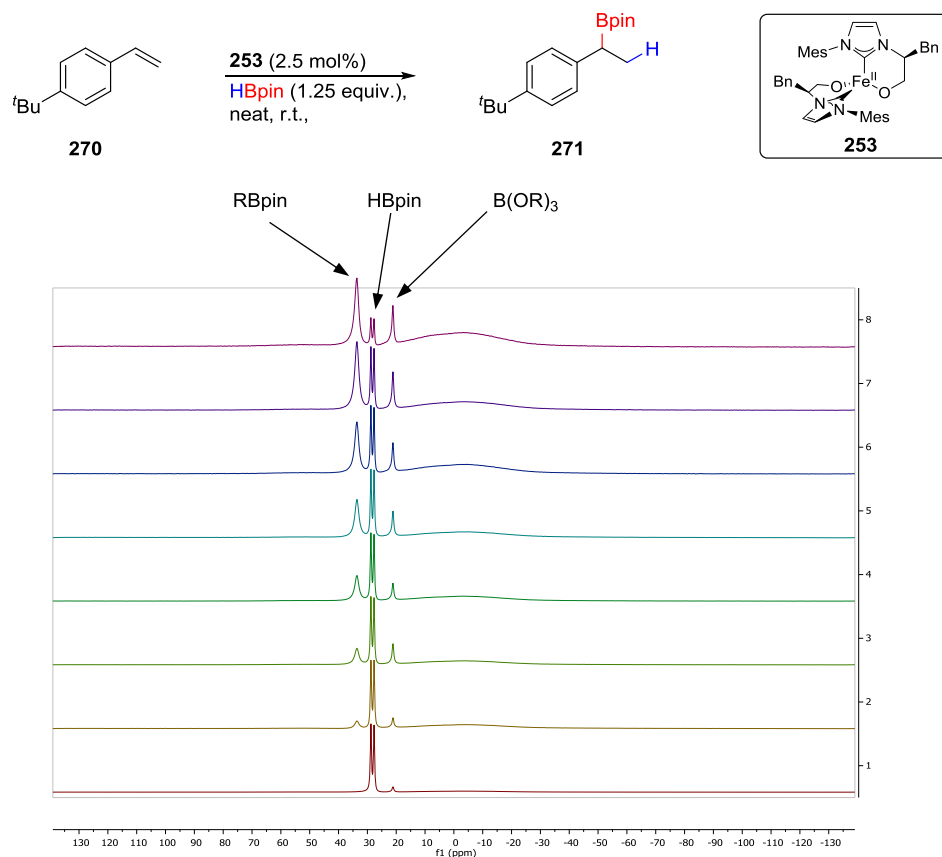
**Figure 4.07** Reaction monitoring of **253** catalysed branched-selective hydroboration of 4-tert-butylstyrene **270** using HBpin. <sup>a</sup>Conversions calculated by <sup>1</sup>H NMR spectroscopy relative to residual starting material. See SI for example of NMR spectra stacks and assignment.

Variation in HBpin **174** loading showed a more complex relationship (Figure 4.08). While increasing the loading of HBpin from 1.0 equivalents to 1.5 equivalents resulted in an increase in yield, there was a corresponding drop-off in the rate of reaction. The reaction with 1.25 equivalents of HBpin reached completion fastest. The reaction with 2.0 equivalents of HBpin however proved to be very slow.



**Figure 4.08** Reaction monitoring of **253** catalysed branched hydroboration of 4-tert-butylstyrene **270** with HBpin. <sup>a</sup>Conversions calculated by <sup>1</sup>H NMR spectroscopy relative to residual starting material.

When  $^{11}\text{B}$  NMR spectroscopy was used to monitor the reaction, consumption of the HBpin **174** (doublet, 28.3 ppm) starting material was observed along with the corresponding formation of alkylboronic esters product **271** (broad singlet, 33.6 ppm). The only other boron-containing species observed were the trialkoxy-boron impurities present in the starting material (singlet, 21.1 ppm). No formation of boron containing side products was observed.



**Figure 4.09** Reaction monitoring by  $^{11}\text{B}$  NMR spectroscopy. Spectra 1-8 correspond to aliquots removed from the reaction mixture and diluted with anhydrous  $\text{CDCl}_3$ , then assessed by  $^1\text{H}$  and  $^{11}\text{B}$  NMR spectroscopy by comparison to authentic samples, at the following time points (0, 5, 15, 30, 60, 120, 240, 1440 mins)



#### 4.4.4.2 Substrate Scope

The scope of the Markovnikov selective hydroboration reaction was next investigated using a range of electronically differentiated styrene derivatives, alkoxy-tethered NHC-Fe<sup>II</sup> **253** (2.5 mol%) and HBpin (1.25 equivalents) (Table 4.4-9). Styrene proved to be an excellent substrate giving the secondary boronic ester **194** in 81% isolated yield, and a 24:1 branched:linear ratio. This represents a significant breakthrough as the highest previously reported branched:linear **194:195** selectivity for an iron-catalysed hydroboration of styrene is 65:35.<sup>426</sup>

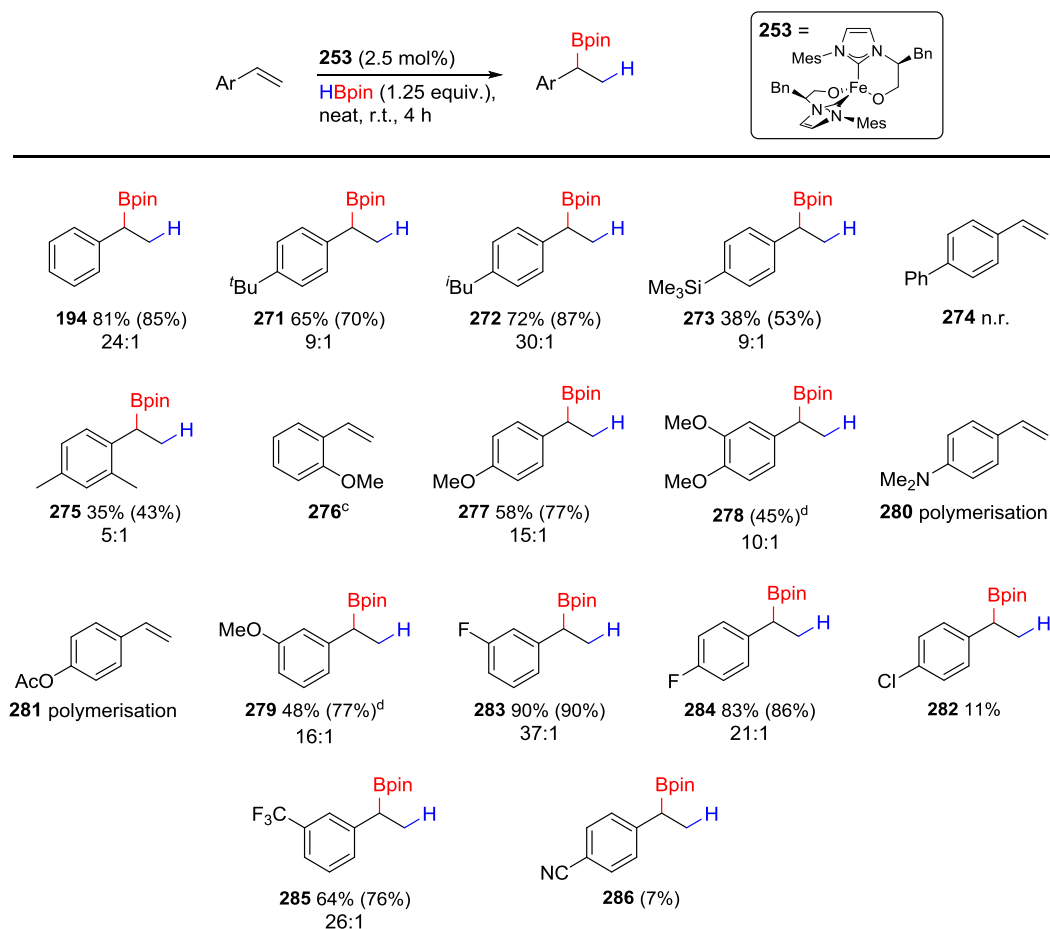
Styrene derivatives bearing alkyl- and trialkylsilyl-substituents reacted in good yields (**271-273**, 38-72% isolated yield) and branched:linear selectivities (9:1 to 30:1). 4-Phenylstyrene **274**, was completely unreactive, presumably due to being solid and having poor solubility in HBpin, and the lack of any other solvent in the developed conditions.

Alkyl substituents could also be tolerated in the *ortho*-position, with synthetically useful yields and branched:linear selectivities achieved (**275**). However incorporation of a methoxy- group in the *ortho* position led to only recovered starting materials (**276**) and the alkene hydrogenation product 1-ethyl-2-methoxybenzene. This was presumably due to the *ortho*-methoxy group disrupting the proposed benzyliron intermediate.

Styrene derivatives bearing electron-donating methoxy- aryl-substituents underwent successful hydroboration in moderate to good yields (35-72%) and selectivities (5:1 to 30:1) to give the branched boronic esters **277-279**. 4-Dimethylaminostyrene **280**, which bears a strongly electron-donating functional group, gave an intractable mixture of polymerisation products,

4-Acetoxyrene **281** and 4-chlorostyrene **282** also gave mixtures of polymerised products, however other examples of styrene derivatives bearing electron-withdrawing aryl-substituents including fluoro- and trifluoromethyl groups gave the secondary alkyl-boronic esters **283-285** in good yields (48-90%) and excellent branched:linear ratios (16:1 to 37:1). Using 4-cyanostyrene resulted in only 7% of the alkene hydroboration product **286**, along with a mixture of alkene and nitrile hydrogenation products.

**Table 4.4-9 253 Catalysed, Markovnikov selective hydroboration of styrene derivatives<sup>a</sup>**



<sup>a</sup>Conditions: HBpin (1.25 equiv.) added in a single portion to **253** (2.5 mol%), followed after ~15 s by an alkene (1 equiv.), r.t., 4 h. Isolated yields following flash column chromatography. Conversions in parentheses, and branched:linear ratios calculated from relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy, average of at least 2 runs. <sup>c</sup>1-ethyl-2-methoxybenzene (20%) observed. <sup>d</sup>Product unstable on silica gel.

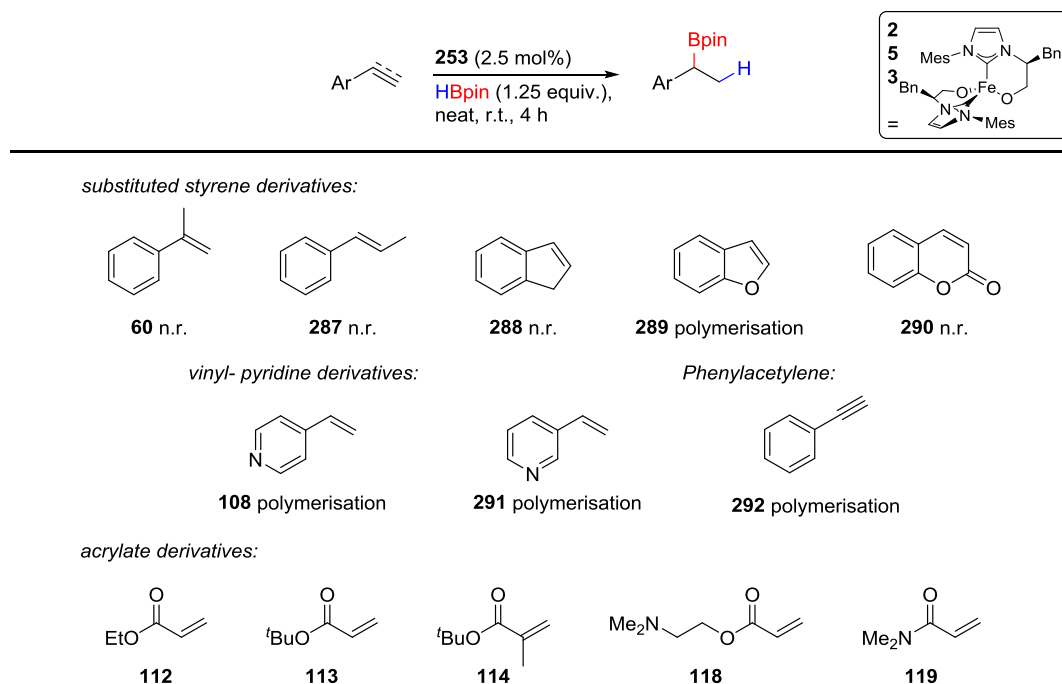
A considerable number of other classes of substrates were investigated under the developed catalytic conditions (Table 4.4-10). Styrene derivatives bearing substituents on the alkenyl-group, including  $\alpha$ -methylstyrene **60** and  $\beta$ -methylstyrene **287** and cyclic derivatives indene **288**, benzofuran **289** and coumarin **290** resulted in no conversion to product, presumably due to steric bulk proximal to the C=C double bond. Coumarin was largely insoluble under the reaction conditions.

Vinylpyridine derivatives **108** and **291** and phenylacetylene **292**, all of which are known to be susceptible to Lewis-acid catalysed polymerisation, gave poorly defined polymers under the developed reaction conditions.

A number of acrylate derivatives **112-114** and **118-119**, which are electronically similar to styrenes and also common polymer precursors, were screened under the developed catalytic conditions and in all cases gave intractable mixture of polymerisation, hydrogenation and C-O cleavage products.

Alkyl- substituted alkenes gave only alkene isomerisation and hydrogenation products, presumably due to not forming stabilised benzyl-iron intermediates (*vide supra*).

**Table 4.4-10 Unsuccessful, **253** Catalysed, Markovnikov selective hydroboration of styrene derivatives<sup>a</sup>**



<sup>a</sup>Conditions: HBpin (1.25 equiv.) added in a single portion to **253** (2.5 mol%), followed after ~15 s by alkene **3** (1 equiv.), r.t., 4 h.

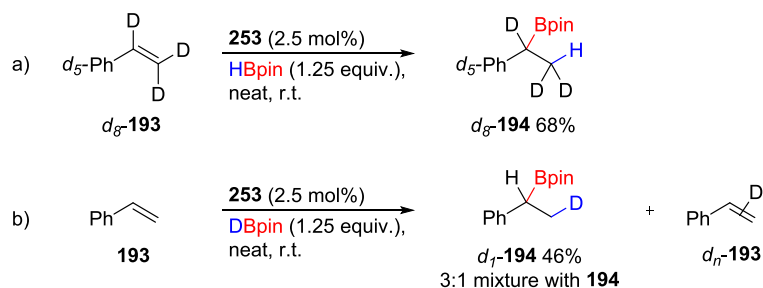
## 4.4.5 MECHANISTIC INVESTIGATIONS

### 4.4.5.1 Deuterium Labelling Experiments

In order to gain insight into the mechanism of the alkene hydroboration with HBpin, deuterium labelling experiments were performed.

Catalytic hydroboration of *d*<sub>8</sub>-styrene with HBpin gave the mono-protio-boronic ester *d*<sub>8</sub>-**194** exclusively with H incorporation at the terminal methyl group (Scheme 4.37 a). When DBpin was used for the hydroboration of styrene the mono-deuterated boronic ester *d*<sub>1</sub>-**194** formed in a 3:1 mixture with the fully protio-boronic ester **194** accompanied by a mixture of deuterio-styrene *d*<sub>n</sub>-**193** derivatives (Scheme 4.37 b).

These results suggest that the reaction proceeds by a hydrometallation of the alkene to give a stabilised benzyliron intermediate and that this hydrometallation precedes C-B bond formation. In addition, the returned deuterio-styrene showed deuterium at both alkene carbons suggesting  $\beta$ -hydride elimination can occur following hydrometallation, as an alternative to B-C bond formation. This  $\beta$ -hydride elimination accounts for the H/D scrambling and for the formation of fully protio-boronic ester observed when using DBpin.



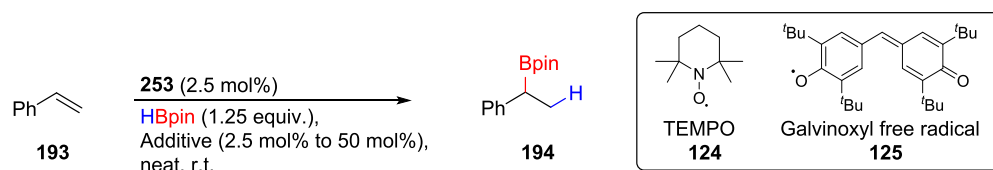
**Scheme 4.37** Deuterium labelling studies of Markovnikov selective alkene hydroboration. Isolated yields following flash column chromatography.

#### 4.4.5.2 Radical Inhibition Experiments

Oxidation of the branched hydroboration product, followed by chiral HPLC analysis revealed no enantioenrichment of the secondary alcohol products, despite the presence of an enantioenriched ligand (see SI for details). While the lack of any enantioenrichment in the products could simply be due to the remoteness of the chiral centre on the ligand, it could also suggest that the reaction proceeds through an alkyl- radical species.

To further probe this aspect of the mechanism, the catalytic hydroboration of styrene with HBpin was performed in the presence of radical inhibitors TEMPO and galvinoxyl free radical. In both cases, increased loading of radical inhibitor was needed to considerably attenuate catalytic activity (Table 4.4-11). The formation of neither alkyl-TEMPO nor alkyl-galvinoxyl adducts was observed by  $^1\text{H}$  NMR spectroscopy or GCMS. Diminished yields in the presence of free radical additives may simply be due to reactions between the additive and the iron catalyst.<sup>276,277</sup> Alternatively, and given the lack of any enantioenrichment in the products, these results could indicate significant radical character to the reaction.

**Table 4.4-11 253-Catalysed, Markovnikov selective hydroboration of styrene: radical inhibition experiments.<sup>a</sup>**



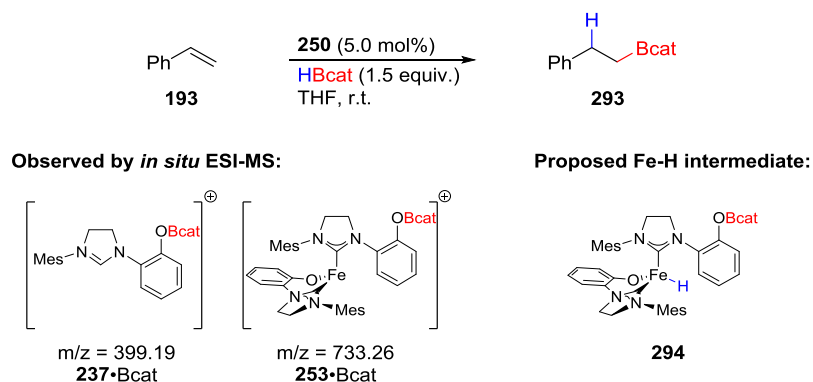
Entry	Radical Inhibitor	(mol%)	Change in Conversion (%) <sup>b</sup>
1	None	-	0
2	TEMPO	2.5	-9
3	TEMPO	10.0	-36
4	TEMPO	25.0	-51
5	TEMPO	50.0	-59
6	Galvinoxyl	2.5	2
7	Galvinoxyl	10.0	-9
8	Galvinoxyl	25.0	-71
9	Galvinoxyl	50.0	-71

<sup>a</sup>Conditions: HBpin (1.25 equiv.) added in a single portion to a mixture of **253** (2.5 mol%) and a radical inhibitor, followed after ~15 s by alkene **193** (1 equiv.), r.t., 4 h. <sup>b</sup>Conversions determined by <sup>1</sup>H NMR spectroscopy and reported relative to that obtained in a control reaction

#### 4.4.5.3 Reaction Monitoring by *In Situ* ESI-MS

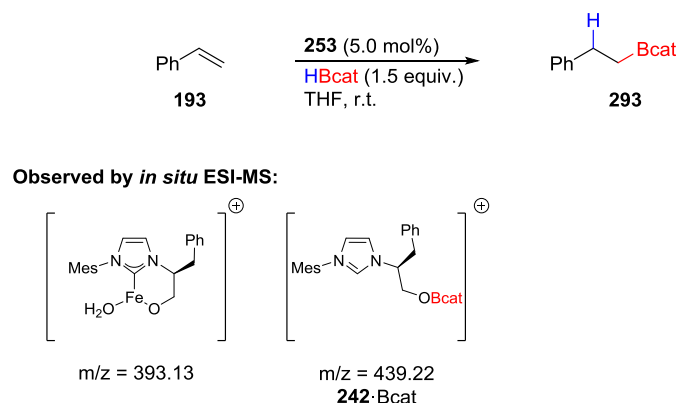
Having proposed that the alkoxy- functionalised NHC ligands of complexes **250-253** could act to provide a ligand-assistance for the heterolytic cleavage of the B-H bond, investigation into the identity of the catalytic intermediates was of paramount importance. *In situ* ESI-MS was used to directly probe the hydroboration reaction mixtures.

In the reaction mixtures of *anti*-Markovnikov selective hydroboration with HBcat, the adduct of aryloxy-tethered NHC Fe<sup>II</sup> complex **250** with Bcat ( $m/z = 733.26$ ) was observed, along with the borylated ligand **237**·Bcat adduct ( $m/z = 399.19$ ) (Scheme 4.38).



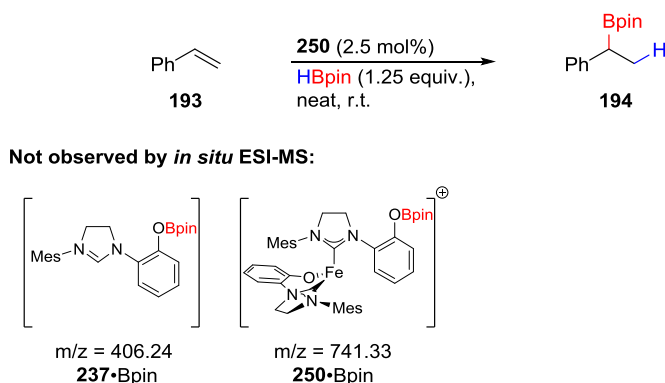
**Scheme 4.38** Complex **253** catalysed, *anti*-Markovnikov selective hydroboration: functionalised ligand **237**·Bcat and complex **253**·Bcat were observed by *in situ* ESI-MS.

Interestingly, when alkoxy-tethered complex **253** was used in conjunction with HBcat, only the Bcat functionalised ligand **242**·Bcat ( $m/z = 439.22$ ) and decomposed complex were observed ( $m/z = 393.13$ ). That no intact or functionalised complexes were observed in this case, may explain why this complex was considerably less active for the *anti*-Markovnikov selective alkene hydroboration (Scheme 4.39).



**Scheme 4.39** Complex **253** catalysed, *anti*-Markovnikov selective hydroboration: functionalised ligand **242**·Bcat and complex decomposition products were observed by *in situ* ESI-MS.

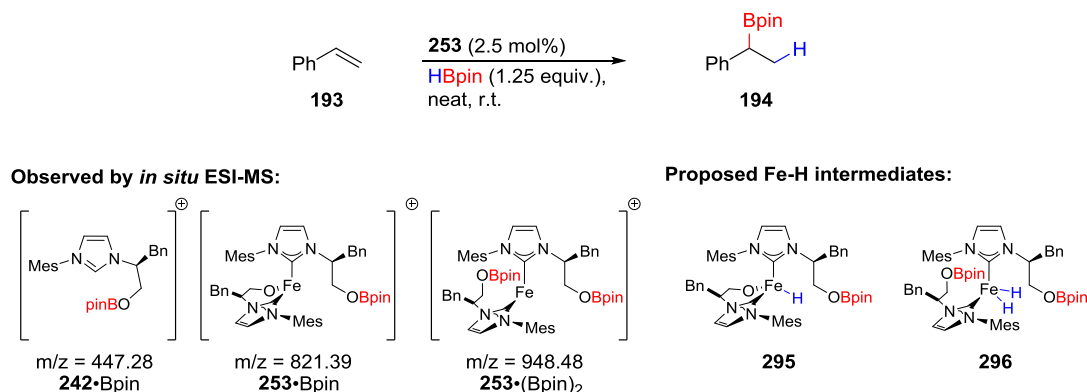
While complex **250** has been shown to catalyse the Markovnikov-selective hydroboration of styrene-derivatives (*vide supra*) it is considerably less active than complex **253**. Interestingly, when the **250** catalysed hydroboration of styrene with HBpin was monitored with ESI-MS, no adducts between HBpin and either the ligand **237** or complex **250** were observed (Scheme 4.40). The only identifiable fragments came from decomposition of the complex. Absence of evidence for the adducts is not evidence of their absence, but this result suggests that the aryloxy-tethered complex **250** is less able to activate HBpin.



**Scheme 4.40** Complex **250** catalysed, Markovnikov selective hydroboration: no functionalised complexes were observed by *in situ* ESI-MS.

Reaction monitoring of the Markovnikov selective hydroboration of styrene **193** with HBpin resulted in the observation of: adducts of alkoxy-tethered NHC-Fe<sup>II</sup> complex **253** with both 1

and 2 equivalents of Bpin ( $m/z = 821.39$  and  $948.48$  respectively), along with the dissociated ligand as an adduct with Bpin, **242**·Bpin ( $m/z = 447.28$ , Scheme 4.41). In reaction mixtures of the Markovnikov selective hydroboration of 4-methoxystyrene the same borylated complexes were observed (see SI for further details), indicating that the formation of these species is not substrate dependent.



**Scheme 4.41** Complex **253** catalysed, anti-Markovnikov selective hydroboration: functionalised ligand **242**·Bpin and complexes **253**·Bpin and **253**·(Bpin)<sub>2</sub> were observed by *in situ* ESI-MS.

That the reaction conditions effectively catalyse the isomerisation of terminal alkyl-substituted alkenes (*vide supra*) strongly implies that the reaction proceeds by alkene hydrometallation by an iron-hydride complex. It is proposed that the observed borylated iron complexes **250**·Bcat, **253**·Bpin and **253**·(Bpin)<sub>2</sub> are derived from the corresponding iron-hydride complexes **294**–**296**. The observation of borylated ligands **237**·Bcat and **242**·Bpin rules out conventional oxidative addition reaction and implies the importance of the non-innocent ligand in assisting the B–H bond cleavage and generating the proposed iron-hydride species.

It should be noted that the ESI-MS provides no data on the regiochemistry of the metallocycle ring-opening on proceeding from complex **253** to the proposed iron-hydride complex **295**. The structure of the ring-opened complex **295** is proposed due to the oxophilicity of boron.

Given that in the Markovnikov selective hydroboration reaction mixtures, both **253**·Bpin and **253**·(Bpin)<sub>2</sub> are observed, and that ESI-MS is not a quantitative technique, it is not clear whether the reaction proceeds by a single catalytic iron-hydride species or an ensemble thereof.

Unfortunately, further mechanistic investigations were not possible due to time constraints.

## 4.5 CONCLUSIONS AND FUTURE WORK

In summary, a series of novel iron(II) complexes bis-ligated by aryloxy- tethered NHC ligands **250-253** have been developed. Aryloxy-tethered NHC-Fe<sup>II</sup> complex **250** has been shown to be an effective catalyst for the *anti*-Markovnikov (linear) selective hydroboration of terminal alkenes using HBcat. Additionally, alkoxy-tethered NHC-Fe<sup>II</sup> complex **253** is the first reported iron catalyst that is effective for the Markovnikov (branched) selective hydroboration of styrene derivatives using HBpin. Both these hydroboration reactions proceed in short reaction times at ambient temperatures and, most significantly, in the absence of any external activator.

Mechanistic investigations suggest that the innovative ligand design facilitates a ligand-assisted catalyst activation, generating the proposed catalytically active iron-hydride species, and eliminating the need for an activating reagent such as those required for other iron-catalysed alkene hydroboration reactions.

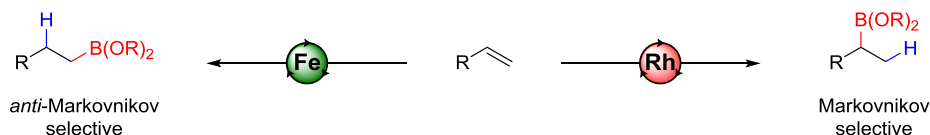
For the *anti*-Markovnikov selective hydroboration reaction, using aryloxy- tethered complex **250** with the more reactive hydroboration reagent HBcat, the cause of the observed regioselectivity is not readily apparent. The reaction may proceed by the formation of a kinetically-favored terminal alkyl-iron intermediate following alkene hydroboration by the proposed iron-hydride species **294**. However, given the complex decomposition observed, a Lewis acid/base promoted,<sup>411</sup> or radical hydrogen-atom transfer reaction is entirely feasible.<sup>123</sup>

The regioselectivity of the Markovnikov selective hydroboration of styrene derivatives with HBpin and alkoxy-tethered complex **253** can be rationalised by the formation a stabilised benzyl-iron intermediate following alkene hydrometallation by proposed iron-hydride complexes **295** and/or **296**.

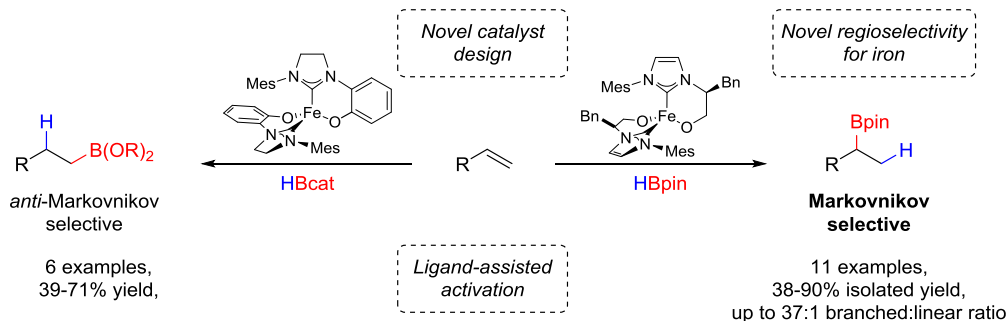
This work represents an significant breakthrough in the relatively young field of iron-catalysed alkene hydroboration, introducing a novel class of catalysts and completely novel regioselectivity (Scheme 4.42).



**The Prior Art:** Iron-catalysed hydroboration give only linear selectivity



**This work:** Iron-catalysed hydroboration with controllable and switchable regioselectivity



**Scheme 4.42** Summary of iron-catalysed alkene hydroboration reactions developed in this project.

However the branched hydroboration reaction is not yet fully developed into a practical, general reaction: the catalysts are of limited air- and moisture stability; the branched-selective hydroboration reaction only tolerates styrene derivatives; and neat reaction conditions are required, further limiting the substrate scope.

Future work should therefore focus on gaining greater understanding of the ligand-assisted catalyst activation, allowing modification and refinement of the ligand design to further optimise the reaction. The highly modular ligand synthesis is well suited to generating diverse libraries of ligands, and this project has only been able to explore a very small number of the possible variants of steric and electronic bulk around these ligands. The targets for such optimisation should be: increased air- and moisture stability of the pre-catalysts; increased substrate scope to include both alkyl- alkenes and greater functional group tolerance; and developing reaction conditions tolerant of solvents. Studies towards isolating the proposed iron-hydride intermediates, or analogues thereof, would be extremely interesting, albeit synthetically very challenging.

Additionally, the developed family of iron(II) NHC complexes could be applied to the activation of other B-X bonds. In particular the activation of C-B bonds, for reactions such as alkene or alkyne carboration.

This work has been published in ACS Catalysis (*ACS Catal.*, **2016**, *6*, 7217–7221, 10.1021/acscatal.6b02281, see Appendix 1)

## CHAPTER 5: EXPERIMENTAL

### 5.1 GENERAL EXPERIMENTAL

All air- and moisture sensitive reactions were carried out either using standard vacuum line and Schlenk techniques under a purified nitrogen atmosphere, or in a glovebox (Innovative Technology) under a purified argon atmosphere. All glassware was cleaned using base (KOH, *t*-PrOH) and acid (HCl<sub>(aq)</sub>) baths, and dried in an oven (180 °C) overnight. Room temperature (r.t.) was set at 25 ± 3 °C. Brine refers to a saturated solution of sodium chloride in deionised water.

Iron(III) trifluoromethanesulfonate 90% was purchased from Sigma Aldrich Co. LLC (lot #SHBB6947V). Iron(III) chloride anhydrous, powder, ≥ 99.99% trace metals basis was purchased from Sigma Aldrich Co. LLC (batch #MKBG2975V). Sodium borohydride powder ≥ 98% was purchased from Sigma Aldrich Co. LLC, (lot #STBC6399V). Iron(II) bromide was purchased from Strem Chemicals Inc. (UK) (lot# A7968079). Other reagents were purchased from Acros Organics, Alfa Aesar, Fluorochem, Sigma Aldrich or Tokyo Chemical Industries UK and used without further purification or synthesised within the laboratory according to literature protocols, except in the following cases:

- Catechol borane was purchased from Acros Organics, Alfa Aesar or Sigma Aldrich and distilled under reduced pressure immediately before use (20 mbar, 40 °C).
- Sodium bis(trimethylsilyl)amide was purchased as a solution in tetrahydrofuran from Sigma Aldrich and titrated, in a modification of literature procedures, against a standard solution of menthol (0.5 M) in anhydrous tetrahydrofuran with 4-phenylbenzylidene as the indicator.<sup>464</sup>

All solvents for air- and moisture sensitive techniques were obtained from an anhydrous solvent system (Innovative Technology). Tetrahydrofuran (Fisher, HPLC grade) was dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Ethanol (absolute) was prepared by distillation from magnesium, under an atmosphere of nitrogen. Anhydrous *d*<sub>8</sub>-tetrahydrofuran and *d*<sub>6</sub>-benzene were prepared by distillation from sodium/benzophenone. Solvents for filtrations, transfers, chromatography and recrystallisation not performed using air- and moisture sensitive techniques were of ACS grade and used without further purification.

All  $^1\text{H}$ ,  $^2\text{H}$ ,  $^{11}\text{B}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ ,  $^{29}\text{Si}$  and  $^{31}\text{P}$  spectra were obtained on Bruker Avance III 400, 500 and 600 MHz spectrometers or a Bruker Avance I 600 MHz spectrometer. All spectra were obtained at ambient temperature. The chemical shifts ( $\delta$ ) are recorded in parts per million (ppm). Coupling constants ( $J$ ) are recorded in hertz (Hz) and rounded to the nearest 0.1 Hz. Multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sex. = sextet, sep. = septet, non. = nonet, m = multiplet, br. s = broad singlet, app. = apparent) and coupling constants are reported where applicable.  $^1\text{H}$  and  $^{13}\text{C}$  Spectra were referenced relative to the residual solvent peak:  $\text{CDCl}_3$  7.27 ppm, 77.2 ppm;  $\text{CD}_2\text{Cl}_2$  5.32 ppm, 53.8 ppm;  $\text{CD}_3\text{CN}$  1.94 ppm, 118.3 ppm;  $\text{C}_6\text{D}_6$  7.16 ppm, 128.1 ppm;  $d_8$ -THF 3.58, 1.72 ppm, 67.2, 25.3 ppm.  $^1\text{H}$  and  $^{13}\text{C}$  assignments are corroborated through DEPT 135 and 2D NMR spectroscopy experiments (COSY, HSQC, HMBC, included where appropriate).

Thin layer chromatography was performed on aluminium backed silica plates (Merck 60 F<sub>254</sub>). Petroleum spirit refers to petroleum ether distillate obtained at 40-60 °C. Product spots were visualised by UV light at 254 nm, and was subsequently developed using potassium permanganate solution, vanillin solution or iodine as appropriate. Flash chromatography was performed on silica gel (Merck Geduran Si 60, 40-63  $\mu\text{m}$ ), quantities of silica, column diameter and solvent system are all reported in the text. Alternatively, flash chromatography was performed using a Biotage Isolera<sup>TM</sup> system and SNAP KP-Sil cartridges.

Catalytic reactions were assayed by  $^1\text{H}$  NMR spectroscopy and/or Gas Chromatography Mass Spectrometry (GCMS) by comparison with authentic samples. GCMS analysis was performed either on a Shimadzu QP2010 SE equipped with a Zebron ZB5-HT column (30.0 m  $\times$  0.25 mm  $\times$  0.25  $\mu\text{m}$ ), or on a Fisons Instruments GC8000 series equipped with a ThermoFisher Scientific Trio1000 series mass spectrometer. Method used: injector temperature of 250 °C; 50 °C for 2 min; ramp 20 °C/min to 300 °C; hold for 2 min.

Chiral HPLC separations were performed on a Shimadzu LC-20AT equipped with an SPD-20A UV-Vis detector and Daicel Chiralpak IB column (250 mm length  $\times$  4.6 mm  $\varnothing$ , particle size 5  $\mu\text{m}$ ), solvent systems and retention times are reported in the text.

Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected.

Infra-red spectra were obtained using a Shimadzu IRAffinity-1 spectrometer (serial no. A213747). Peaks are reported in  $\text{cm}^{-1}$ .

Spectra for *in situ* reaction monitoring by ESI-MS were collected on an Advion Expression CMS operating in positive mode. Sampling was performed manually inside a glovebox *via* a capillary

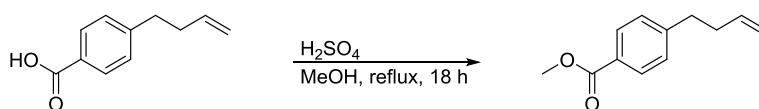
attached to the spectrometer. Isotope abundance for each compound was predicted using ChemDraw Prime 15.1.

X-ray crystallography was performed by the University of Edinburgh, X-ray Crystallography Service. Crystals suitable for X-ray crystallography were mounted on a MITIGEN holder in Paratone oil and spectra were obtained on either an Agilent Technologies SuperNova diffractometer or a Bruker SMART APEXII diffractometer. Crystals were kept at  $T = 120.0$  K during data collection. Using **Olex2**<sup>465</sup> the structure was solved with either: the SIR2008 structure solution program, using the Direct Methods solution method; or the **ShelXS**<sup>466</sup> structure solution program, using the Patterson solution method. The model was refined with version of **ShelXL**<sup>2</sup> using Least Squares minimisation.

High resolution mass spectra were collected by the University of Edinburgh, School of Chemistry, Mass Spectrometry Laboratory. Electron Ionisation (EI) mass spectra were obtained using a Thermo/Finnigan MAT 900 Sector instrument. Electrospray Ionisation (ESI) mass spectra were obtained using a Bruker micrOTOF II spectrometer. Data are reported in the form of  $m/z$  of parent (molecular) ions ( $[M]^+$  or  $[M+H/Na]^+$ ).

## 5.2 PREPARATION OF ALKENE DERIVATIVES

### 4-(3-buten-1-yl)-benzoic acid, methyl ester<sup>417</sup>



A solution of 4-(3-butenyl)-benzoic acid (0.528 g, 3.00 mmol) and sulphuric acid (10 drops) in methanol (15 mL) under a nitrogen atmosphere was heated under reflux for 18 hours. Aqueous sulphate buffer solution (15 mL) was added and the organic phase was extracted with ethyl acetate ( $3 \times 10$  mL), washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. Following flash column chromatography (conditions: silica, 30 g; 30 mm Ø; hexane/diethyl ether 80:20 v/v over 10 column volumes), 4-(3-butenyl)-benzoic acid methyl ester was isolated as a colourless oil (0.400 g, 2.10 mmol, 70%).

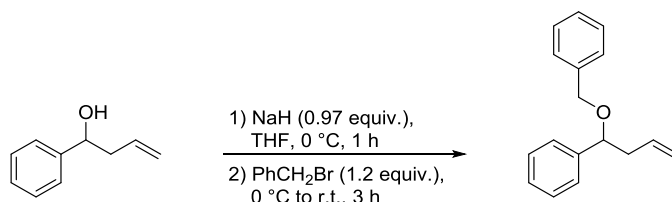
$R_f = 0.47$  (petroleum spirit/diethyl ether, 80:20 v/v)

$\delta_H$  (500 MHz,  $CDCl_3$ ) 7.98 (dt,  $J = 8.3, 1.8$  Hz, 2H, ArH), 7.28 (app. d,  $J = 8.3$  Hz, 2H, ArH), 5.91-5.81 (m, 1H,  $CH_2CH$ ), 5.10-4.99 (m, 2H,  $CHCH_2$ ), 3.93 (s, 3H,  $OCH_3$ ), 2.79 (t,  $J = 7.5$  Hz, 2H,  $ArCH_2$ ), 2.42 (app. q,  $J = 7.9$  Hz, 2H,  $CH_2CH$ ).

$\delta_C$  (125 MHz,  $CDCl_3$ ) 167.2 (C), 147.4 (C), 137.5 (CH), 129.7 (CH), 128.5 (CH), 127.9 (C), 115.4 (CH<sub>2</sub>), 52.0 (CH<sub>3</sub>), 35.4 (CH<sub>2</sub>), 35.1 (CH<sub>2</sub>).

Data in accordance with that previously reported.<sup>417</sup>

### 1-Benzyloxy-1-phenyl-3-butene<sup>467</sup>



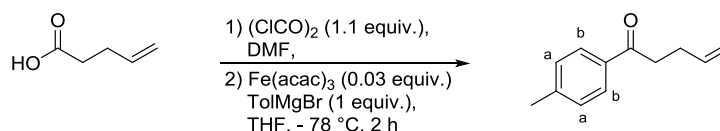
A solution of 4-phenyl-1-buten-4-ol (0.425 g, 2.90 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise to solution of sodium hydride (0.120 g, 3.00 mmol) in anhydrous tetrahydrofuran (10 ml) being stirred under an atmosphere of nitrogen at 0 °C. The reaction mixture was stirred for 1 hour, then benzyl bromide (0.598 g, 3.50 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. After 3 hours triethylamine (0.354 g, 3.50 mmol) was added and the reaction mixture concentrated *in vacuo*. The reaction mixture was diluted with saturated ammonium chloride solution (10 mL) with dichloromethane (10 mL). The organic phase was extracted with diethyl ether (3 × 10 mL), washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. Following flash column chromatography (conditions: silica, 30 g; 30 mm Ø; pentane/diethyl ether 99:1 v/v over 10 column volumes), 1-benzyloxy-1-phenyl-3-butene was isolated as a colourless oil (0.604 g, 0.60 mmol, 21%).

$\delta_H$  (500 MHz,  $CDCl_3$ ) 7.43- 7.29 (m, 10H, Ar $H$ ), 5.87-5.78 (m, 1H, CH<sub>2</sub>CH $H$ ), 5.10-5.02 (m, 2H, CHCH<sub>2</sub>), 4.50 (d,  $J$  = 11.9 Hz, 1H, OCH<sup>a</sup>H<sup>b</sup>Ph), 4.40 (t, 6.2 Hz, 1H, PhCHO), 4.31 (d,  $J$  = 11.9 Hz, 1H, OCH<sup>a</sup>H<sup>b</sup>Ph), 2.67 (app. quin.,  $J$  = 6. 8 Hz, 1H, CHCH<sup>a</sup>H<sup>b</sup>), 2.47 (app. quin.,  $J$  = 7.1 Hz, 1H, CHCH<sup>a</sup>H<sup>b</sup>).

$\delta_C$  (125 MHz,  $CDCl_3$ ) 141.9 (C), 138.5 (C), 134.9 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 116.9 (CH<sub>2</sub>), 81.2 (CH), 70.4 (CH<sub>2</sub>), 42.7 (CH<sub>2</sub>).

Data in accordance with that previously reported.<sup>467</sup>

### 1-(4-Methylphenyl)-4-penten-1-one<sup>468</sup>



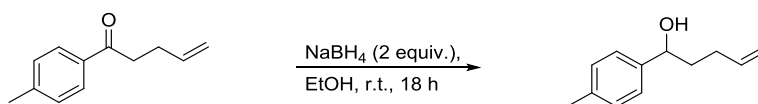
*N,N*-dimethylformamide (2 drops) was added dropwise to a rapidly stirred mixture of pentenoic acid (2.503 g, 25.00 mmol) and oxalyl chloride (3.427 g, 27.00 mmol). Once bubbling had ceased, further *N,N*-dimethylformamide (2 drops) was added, the reaction mixture was diluted with hexanes (10 mL), filtered through celite and concentrated *in vacuo*. The resulting colourless oil was diluted with anhydrous tetrahydrofuran (20 mL) and cooled to  $-78\text{ }^{\circ}\text{C}$ , to this solution was added dropwise a mixture of *p*-tolylmagnesium bromide (1 M in tetrahydrofuran, 25 mL, 25 mmol) and iron(III) acetylacetonate (0.265 g, 0.75 mmol) in tetrahydrofuran (20 mL), under a nitrogen atmosphere, and also at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 2 hours under a nitrogen atmosphere, then diluted with hydrochloric acid (1 M, 20 mL). The organic phase was extracted with diethyl ether ( $3 \times 10\text{ mL}$ ), washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The product was isolated, following flash column chromatography (conditions: silica, 200 g, 50 mm Ø; gradient petroleum spirit/ethyl acetate, from 99:1 to 9:1 v/v over 10 column volumes), as a pale yellow oil (0.881 g, 5.57 mmol, 23%).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.89 (d,  $J = 8.3\text{ Hz}$ , 2H, ArH<sup>a</sup>), 7.28 (d,  $J = 8.0\text{ Hz}$ , 2H, ArH<sup>b</sup>), 5.93 (ddt,  $J = 16.9, 10.2, 6.6\text{ Hz}$ , 1H, CH<sub>2</sub>CH), 5.14–5.01 (m, 2H, CHCH<sub>2</sub>), 3.07 (t,  $J = 7.3\text{ Hz}$ , 2H, COCH<sub>2</sub>), 2.51 (m, 2H, CH<sub>2</sub>CH), 2.43 (s, 3H, CH<sub>3</sub>).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 199.1 (C), 143.8 (C), 137.4 (CH), 134.5 (C), 129.3 (CH), 128.2 (CH), 115.2 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>).

Data in accordance with that previously reported.<sup>468</sup>

### 1-(4-Methylphenyl)-4-penten-1-ol<sup>469</sup>



A solution of 1-(4-methylphenyl)-4-penten-1-one (0.871 g, 5.00 mmol) in ethanol (20 mL) was added to NaBH<sub>4</sub> (0.379 g, 10.00 mmol) and the resulting mixture was stirred under nitrogen for 18 hours. The reaction mixture was diluted with hydrochloric acid (1 M, 20 mL). The organic phase was extracted with diethyl ether ( $3 \times 10\text{ mL}$ ), washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The product was isolated, by flash column chromatography

(conditions: silica 50 g; 50 mm Ø; petroleum spirit/diethyl ether, 80:20 v/v over 10 column volumes), as a colourless oil (0.729 g, 4.14 mmol, 83%).

$R_f = 0.17$  (petroleum spirit/diethyl ether, 95:5 v/v)

$\delta_H$  (500 MHz,  $CDCl_3$ ) 7.27 (d,  $J = 8.1$  Hz, 2H, ArH), 7.19 (d,  $J = 7.8$  Hz, 2H, ArH), 5.87 (ddt,  $J = 17.10, 10.32, 3.63$  Hz, 1H,  $CH_2CH$ ), 5.10-4.99 (m, 2H,  $CHCH_2$ ), 4.69 (m, 1H, ArCH), 2.38 (s, 3H,  $CH_3$ ), 2.24-2.08 (m, 2H,  $CH_2$ ), 1.97-1.79 (m, 2H,  $CH_2$ ).

$\delta_C$  (125 MHz,  $CDCl_3$ ) 141.7 (C), 138.3 (CH), 137.3 (C), 129.2 (CH), 125.9 (CH), 114.9 ( $CH_2$ ), 73.9 (CH), 38.0 ( $CH_2$ ), 30.1 ( $CH_2$ ), 21.1 ( $CH_3$ ).

Data in accordance with that previously reported.<sup>469</sup>

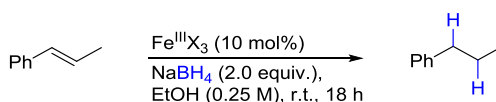
### 5.3 ALKENE HYDROGENATION WITH $NABH_4$ : REACTION OPTIMISATION

All reactions were carried out at room temperature in a Radley's carousel multiple position reactor under a nitrogen atmosphere.

#### General procedure A

A solution of 1-phenyl-4-butene (0.066 g, 0.50 mmol, 1.00 equivalent) or *trans*- $\beta$ -methylstyrene (0.0661g, 0.50 mmol, 1.00 equivalent) in anhydrous ethanol (2 mL) was added to a mixture an iron salt (0.05 to 0.50 mmol, 0.10 to 1.00 equivalents) and sodium borohydride (0.038 g, 1.00 mmol, 2.00 equivalents). The resulting mixture was stirred under a nitrogen atmosphere for 18 h. Aqueous hydrochloric acid (1 M, 10 mL) was added, and the aqueous phase extracted with diethyl ether ( $2 \times 10$  mL) and pentane (10 mL). The combined organic layers were then washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (0.017 g, 0.10 mmol, 0.20 equivalents) was added as internal standard, and the crude product mixture was analysed by  $^1H$  NMR spectroscopy and GCMS.

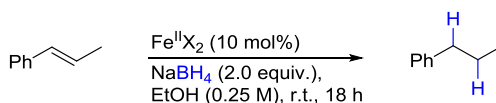
**Table 5.3-1 Screening of iron(III) salts with NaBH<sub>4</sub> for *trans*- $\beta$ -methylstyrene<sup>a</sup>**



Entry	Iron Salt	Conversion (%) <sup>b</sup> Hydrogenation product
1	FeF <sub>3</sub> ·3H <sub>2</sub> O	0
2	FeCl <sub>3</sub>	2
3	FeBr <sub>3</sub>	2
4	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	2
5	Fe(acac) <sub>3</sub>	0
6	Fe <sub>2</sub> O <sub>3</sub>	0
7	Fe(OTf) <sub>3</sub>	1
8	Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·6H <sub>2</sub> O	0
9	FePO <sub>4</sub> ·4H <sub>2</sub> O	0
10	Fe <sup>III</sup> citrate	0
11	Fe(OH)O	0
12	Fe <sup>III</sup> (p-tolsyl) <sub>3</sub>	1
13	K <sub>3</sub> Fe(CN) <sub>6</sub>	0

<sup>a</sup>Conditions: *trans*- $\beta$ -methylstyrene (1.0 equiv.) in ethanol (2 mL) was added to an iron(III) salt (0.1 equiv.) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR spectroscopy.

**Table 5.3-2 Screening of iron(II) salts with NaBH<sub>4</sub> for *trans*- $\beta$ -methylstyrene<sup>a</sup>**



Entry	Iron Salt	Conversion (%) <sup>b</sup> Hydrogenation product
1	FeF <sub>2</sub>	1
2	FeF <sub>2</sub> ·4H <sub>2</sub> O	0
3	FeCl <sub>2</sub>	1
4	FeBr <sub>2</sub>	1
5	FeI <sub>2</sub>	1
6	Fe(OTf) <sub>2</sub>	1
7	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	1
8	Fe(acac) <sub>2</sub>	1
9	Fe(OAc) <sub>2</sub>	0
10	Fe(SO <sub>4</sub> )	1
11	Fe <sup>II</sup> (C <sub>2</sub> O <sub>4</sub> )·2H <sub>2</sub> O	3
12	Fe <sup>II</sup> (MoO <sub>4</sub> )	2
13	K <sub>4</sub> Fe(CN) <sub>6</sub>	0
14	Ferrocene	0

<sup>a</sup>Conditions: *trans*- $\beta$ -methylstyrene (1.0 equiv.) in ethanol (2 mL) was added to an iron(II) salt (0.1 equiv.) and sodium borohydride (2.0 equiv.), r.t., 18 h. <sup>b</sup>Conversion measured by relative integrals of starting material and product peaks in <sup>1</sup>H NMR.



## 5.4 ALKENE HYDROGENATION WITH $\text{NaBH}_4$ : ISOLATED PRODUCTS

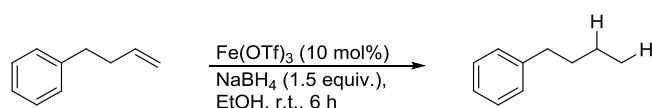
### General procedure B

A solution of iron(III) triflate (0.050 g, 0.10 mmol, 0.10 equivalents) in anhydrous ethanol (2 mL) was added to a solution of a terminal alkene derivative (1.00 mmol, 1.00 equivalent) and sodium borohydride (0.057 g, 1.50 mmol, 1.50 equivalents) in anhydrous ethanol (2 mL). The resulting mixture was stirred under a nitrogen atmosphere for 6 h. The reaction mixture was diluted with a saturated solution of sodium hydrogen carbonate (10 mL) and the aqueous phase was extracted with dichloromethane ( $3 \times 10$  mL). The combined organic layers were then washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (0.017 g, 0.10 mmol, 0.20 equivalents) was added as internal standard, and the crude product mixture was analysed by  $^1\text{H}$  NMR spectroscopy and GCMS.

In the case of products requiring further purification, the following procedure (**C**) was used to facilitate separation by flash column chromatography:<sup>470</sup>

The crude product mixture was diluted with dichloromethane (5 mL), *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol, 1.00 equivalent) added, and the resulting mixture was stirred for 16 h. Sodium sulphite was added, and the reaction mixture was diluted with aqueous hydrochloric acid (1 M, 10 mL) and the aqueous phase was extracted with dichloromethane ( $3 \times 10$  mL). The combined organic layers were then washed with brine, dried with magnesium sulfate and concentrated *in vacuo*.

### Butylbenzene (**66**)<sup>254</sup>



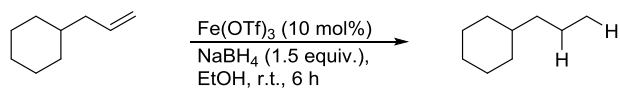
According to general procedure **B**, 4-phenyl-1-butene (0.132 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 99:1 v/v over 5 column volumes) butylbenzene (0.110 g, 0.83 mmol, 83%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.31 (t,  $J = 8.0$  Hz, 2H, ArH), 7.2-7.18 (m, 3H, ArH), 2.65 (t,  $J = 7.8$  Hz, 2H, ArCH<sub>2</sub>), 1.68-1.60 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.40 (app. sex.,  $J = 7.6$  Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.96 (t,  $J = 7.0$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 143.0 (C), 128.5 (CH), 128.3 (CH), 125.6 (CH), 35.7 ( $\text{CH}_2$ ), 33.7 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_2$ ), 14.0 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>254</sup>

### Propylcyclohexane (65)

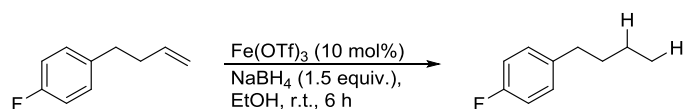


According to general procedure **B**, allylcyclohexane (0.124 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). Propylcyclohexane was obtained as a colourless oil (0.086 g, 0.69 mmol, 69%).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 1.76-1.63 (m), 1.38-1.14 (m), 0.95-0.86 (m).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 39.9 ( $\text{CH}_2$ ), 37.4 (CH), 33.4 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 19.9 ( $\text{CH}_2$ ), 14.4 ( $\text{CH}_3$ ).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 111856).

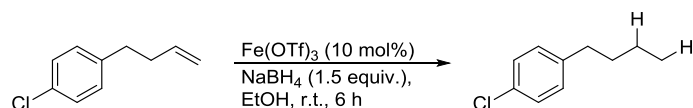
**1-Fluoro-4-butenylbenzene (81)**<sup>471</sup>

According to general procedure **B**, 1-fluoro-4-butenylbenzene (0.150 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 99:1 v/v over 5 column volumes) 1-fluoro-4-butylbenzene (0.120 g, 0.79 mmol, 79%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.17-7.12 (m, 2H, ArH<sup>a</sup>), 6.98 (tt,  $J = 8.8, 2.1$  Hz, 2H, ArH<sup>b</sup>), 2.61 (t,  $J = 7.9$  Hz, 2H, ArCH<sub>2</sub>), 1.64-1.57 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.41-1.33 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.96 (t,  $J = 7.4$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 161.1 (d,  $J = 242.8$  Hz, CF), 138.5 (d,  $J = 3.5$  Hz, C), 129.7 (d,  $J = 8.0$  Hz, CH), 114.9 (d,  $J = 20.9$  Hz, CH), 34.8 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>).

Data in accordance with that previously reported.<sup>471</sup>

**1-Chloro-4-butenylbenzene (82)**<sup>472</sup>

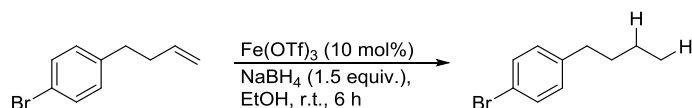
According to general procedure **B**, 1-chloro-4-butenylbenzene (0.166 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 99:1 v/v over 5 column volumes) 1-chloro-4-butylbenzene (0.129 g, 0.79 mmol, 77%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.26 (d,  $J = 8.4$  Hz, 2H, ArH), 7.13 (d,  $J = 8.4$  Hz, 2H, ArH), 2.60 (t,  $J = 7.8$  Hz, 2H, ArCH<sub>2</sub>), 1.64-1.57 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.37 (app. sex.,  $J = 7.5$  Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.95 (t,  $J = 7.4$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 141.3 (C), 131.3 (C), 129.8 (CH), 128.3 (CH), 35.0 ( $\text{CH}_2$ ), 33.6 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_2$ ), 13.9 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>472</sup>

### 1-Bromo-4-butenylbenzene (83)<sup>473</sup>



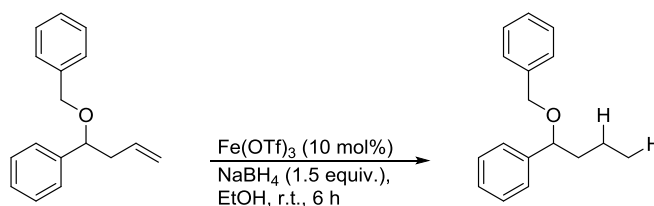
According to general procedure **B**, 1-bromo-4-butenylbenzene (0.210 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 99:1 v/v over 5 column volumes) 1-bromo-4-butylbenzene (0.150 g, 0.71 mmol, 71%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.42 (dt,  $J = 8.5, 2.1$  Hz, 2H, ArH), 7.08 (dt,  $J = 8.3, 2.1$  Hz, 2H, ArH), 2.59 (t,  $J = 7.8$  Hz, 2H, ArCH<sub>2</sub>), 1.64-1.57 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.37 (app. sex.,  $J = 7.7$  Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.95 (t,  $J = 7.4$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 141.8 (C), 131.3 (CH), 130.2 (CH), 119.3 (C), 35.0 ( $\text{CH}_2$ ), 33.5 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 13.9 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>473</sup>

### 1-Benzyloxy-1-phenylbutane (88)<sup>474</sup>



According to general procedure **B**, 1-benzyloxy-1-phenyl-3-butene (0.238g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.50 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 99:1

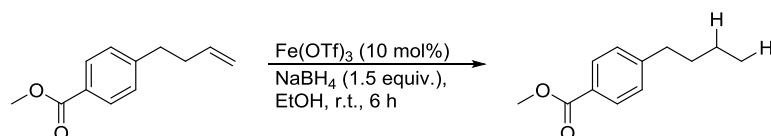
v/v over 10 column volumes) 1-benzyloxy-1-phenyl-3-butane (0.120 g, 0.50 mmol, 50%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (600 MHz,  $\text{CDCl}_3$ ) 7.41-7.29 (m, 10H, ArH), 4.48 (d,  $J = 12.1$  Hz, 1H,  $\text{OCH}^{\text{a}}\text{H}^{\text{b}}$ ), 4.34 (dd,  $J = 7.6, 5.7$  Hz, 1H, PhCHO), 4.28 (d,  $J = 11.7$  Hz, 1H,  $\text{OCH}^{\text{a}}\text{H}^{\text{b}}$ ), 1.93-1.85 (m, 1H,  $\text{ArCH}^{\text{a}}\text{H}^{\text{b}}$ ), 1.69-1.62 (m, 1H,  $\text{ArCH}^{\text{a}}\text{H}^{\text{b}}$ ), 1.53-1.45 (m, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{CH}_3$ ), 1.36-1.29 (m, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{CH}_3$ ), 0.91 (t,  $J = 7.6$  Hz, 3H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{CH}_3$ ).

$\delta_{\text{C}}$  (150 MHz,  $\text{CDCl}_3$ ) 145.5 (C), 141.4 (C), 131.1 (CH), 131.0 (CH), 130.4 (CH), 130.1 (CH), 130.1 (CH), 129.5 (CH), 84.0 ( $\text{CH}_2$ ), 73.1 ( $\text{CH}_2$ ), 43.2 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_2$ ), 16.6 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>474</sup>

#### 4-Butyl-benzoic acid, methyl ester (93)<sup>475</sup>



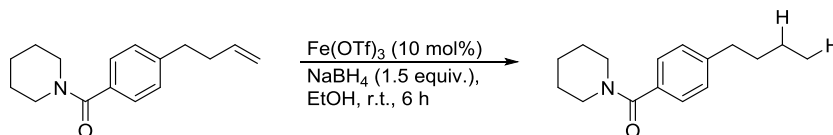
According to general procedure **B**, 4-(3-butenyl)-benzoic acid, methyl ester (0.190 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 9:1 v/v over 10 column volumes) 4-butyl-benzoic acid, methyl ester (0.181 g, 0.94 mmol, 94%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.97 (dt,  $J = 8.4, 1.9$  Hz, 2H, ArH<sup>a</sup>), 7.26 (d,  $J = 8.1$  Hz, 2H, ArH<sup>b</sup>), 3.92 (s, 3H,  $\text{OCH}_3$ ), 2.69 (t,  $J = 7.8$  Hz, 2H, ArCH<sub>2</sub>), 1.68-1.59 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.43-1.35 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 0.95 (t, 7.4 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 148.5 (C), 129.6 (CH), 128.4 (CH), 127.6 (C), 51.9 (CH<sub>3</sub>), 35.7 (CH<sub>2</sub>), 33.3 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>).

Data in accordance with that previously reported.<sup>475</sup>

### 1-(4-Butylbenzoyl)-piperidine (95)



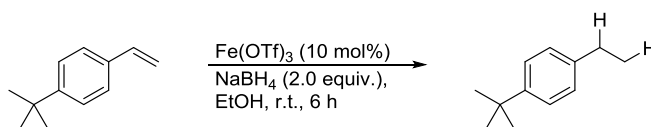
According to general procedure **B**, 1-bromo-4-butenylbenzene (0.243 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum ether/diethyl ether, 7:3 v/v over 10 column volumes) 1-(4-butylbenzoyl)-piperidine (0.202 g, 0.87 mmol, 87%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.32 (d,  $J = 8.1$  Hz, 2H, ArH), 7.21 (d,  $J = 8.2$  Hz, 2H, ArH), 3.72 (br. s, 2H,  $\text{CH}_2$ ), 3.39 (br. s, 2H,  $\text{CH}_2$ ), 2.64 (t,  $J = 7.8$  Hz, 2H, Ar $\text{CH}_2$ ), 1.76 – 1.46 (br. m, 8H), 1.38 (app. sex.,  $J = 7.6$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 0.95 (t,  $J = 7.3$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 170.6 (C), 144.4 (C), 133.8 (C), 128.4 (CH), 126.9 (CH), 48.8 (br. s,  $\text{CH}_2$ ), 43.2 (br. s,  $\text{CH}_2$ ), 35.5 ( $\text{CH}_2$ ), 33.5 ( $\text{CH}_2$ ), 26.6 (br. s,  $\text{CH}_2$ ), 25.7 (br. s,  $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_2$ ), 13.9 ( $\text{CH}_3$ ).

HRMS (EI) Exact mass calculated for  $\text{C}_{16}\text{H}_{23}\text{NO}$  [M]<sup>+</sup>: 245.1780, found: 245.1774.

### 1-Ethyl-4-*tert*-butylbenzene (96)<sup>254</sup>



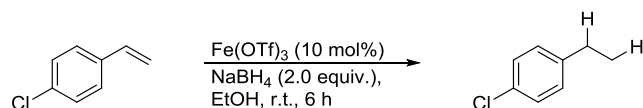
According to general procedure **B**, 4-*tert*-butylstyrene (0.166 g, 1.00 mmol), sodium borohydride (0.076 g, 2.00 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 10 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 1-ethyl-4-*tert*-butylbenzene (0.073 g, 0.45 mmol, 45%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.37 (d,  $J = 8.3$  Hz, 2H, ArH), 7.20 (d,  $J = 8.4$  Hz, 2H, ArH), 2.68 (q,  $J = 7.7$  Hz, 2H, Ar $\text{CH}_2$ ), 1.37 (s, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.29 (t,  $J = 7.7$  Hz,  $\text{C}(\text{CH}_3)_3$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 148.4 (C), 141.2 (C), 127.5 (CH), 125.2 (CH), 34.4 (C), 31.5 ( $\text{CH}_3$ ), 28.3 ( $\text{CH}_2$ ), 15.5 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>254</sup>

#### 1-Ethyl-4-chlorobenzene (100)<sup>254</sup>



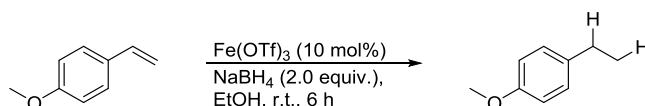
According to general procedure **B**, 4-chlorostyrene (0.139 g, 1.00 mmol), sodium borohydride (0.076 g, 2.00 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 10 g; 30 mm  $\varnothing$ ; pentane/diethyl ether, 99:1 v/v over 10 column volumes) 1-chloro-4-ethylbenzene (0.016 g, 0.12 mmol, 12%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (600 MHz,  $\text{CDCl}_3$ ) 7.25 (dt,  $J = 8.3, 1.9$  Hz, 2H, ArH), 7.13 (m, 2H, ArH), 2.63 (q,  $J = 7.6$  Hz, 2H, Ar $\text{CH}_2$ ), 1.23 (t,  $J = 7.9$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

$\delta_{\text{C}}$  (150 MHz,  $\text{CDCl}_3$ ) 145.3 (C), 133.9 (C), 131.9 (CH), 131.0 (CH), 28.3 ( $\text{CH}_2$ ), 15.5 ( $\text{CH}_3$ ).

Data in accordance with that previously reported.<sup>254</sup>

#### 1-Ethyl-4-methoxybenzene (104)<sup>254</sup>



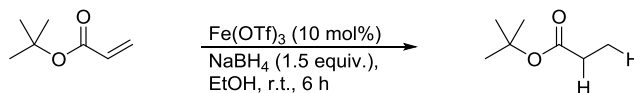
According to general procedure **B**, 4-methoxystyrene (0.134 g, 1.00 mmol), sodium borohydride (0.076 g, 2.00 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). The resulting oil was reacted with *m*-chloroperbenzoic acid (0.248 g, 1.00 mmol) in dichloromethane (5 mL) according to general procedure **C**. Following flash column chromatography (conditions: silica, 10 g; 30 mm  $\varnothing$ ; pentane/diethyl ether, 9:1 v/v over 5 column volumes) 1-ethyl-4-methoxybenzene (0.067 g, 0.49 mmol, 49%) was obtained as a colourless oil.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.16 (dt,  $J = 8.8, 2.1$  Hz, 2H, ArH), 6.88 (dt,  $J = 8.7, 2.1$  Hz, 2H, ArH), 3.83 (s, 3H,  $\text{OCH}_3$ ), 2.64 (q,  $J = 7.7$  Hz, 2H, Ar $\text{CH}_2$ ), 1.26 (t,  $J = 7.7$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 157.7 (C), 136.4 (C), 128.7 (CH), 113.7 (CH), 55.3 ( $\text{CH}_3$ ), 28.0 ( $\text{CH}_2$ ), 16.0 ( $\text{CH}_2$ ).

Data in accordance with that previously reported.<sup>254</sup>

***tert*-Butyl propionate (113)**



According to general procedure **B**, *tert*-butylacetate (0.128 g, 1.00 mmol), sodium borohydride (0.057 g, 1.50 mmol) and iron(III) triflate (0.050 g, 0.10 mmol) were reacted in anhydrous ethanol (4 mL). *tert*-butyl propionate was obtained as a colourless oil (0.096 g, 0.74 mmol, 74%).

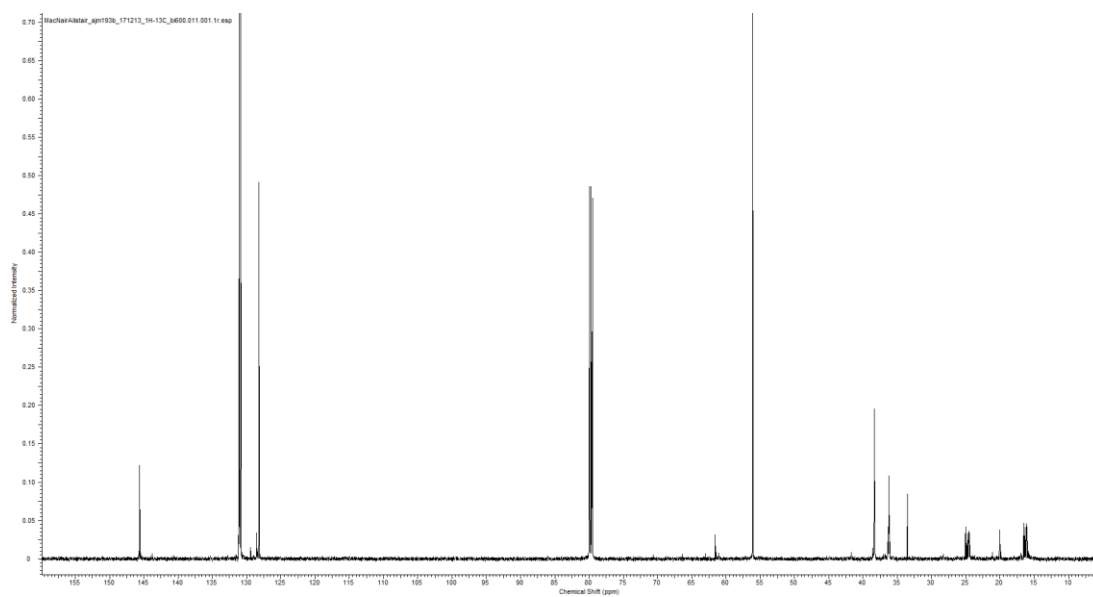
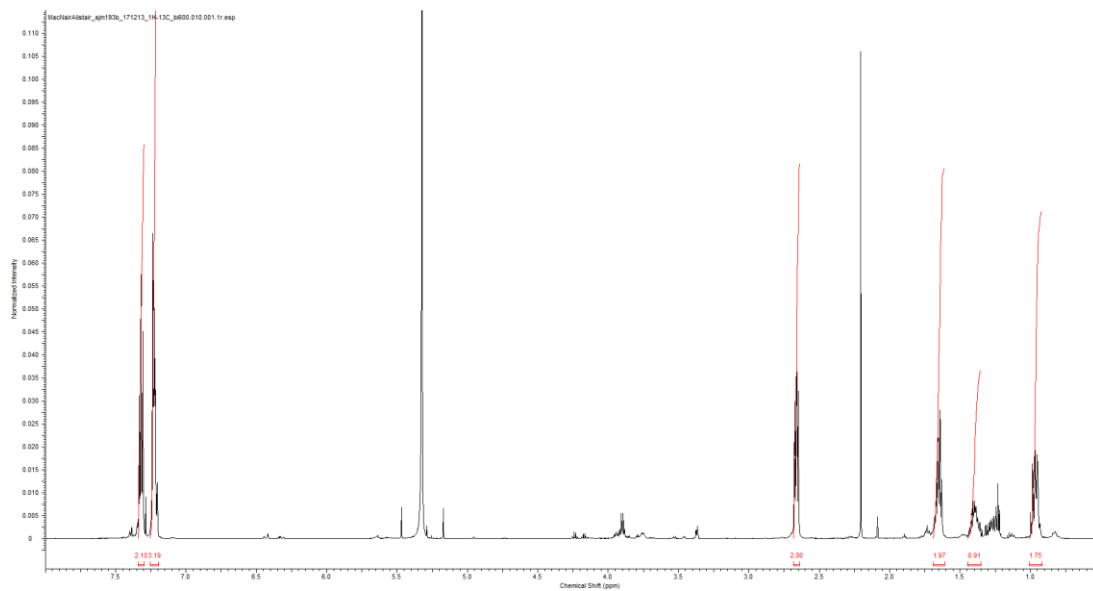
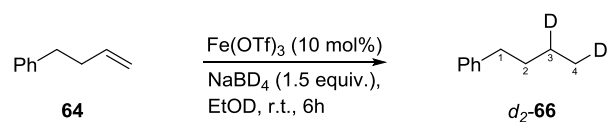
$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 2.25 (q,  $J = 7.5$  Hz, 2H,  $\text{COCH}_2$ ), 1.46 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.11 (t,  $J = 7.6$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

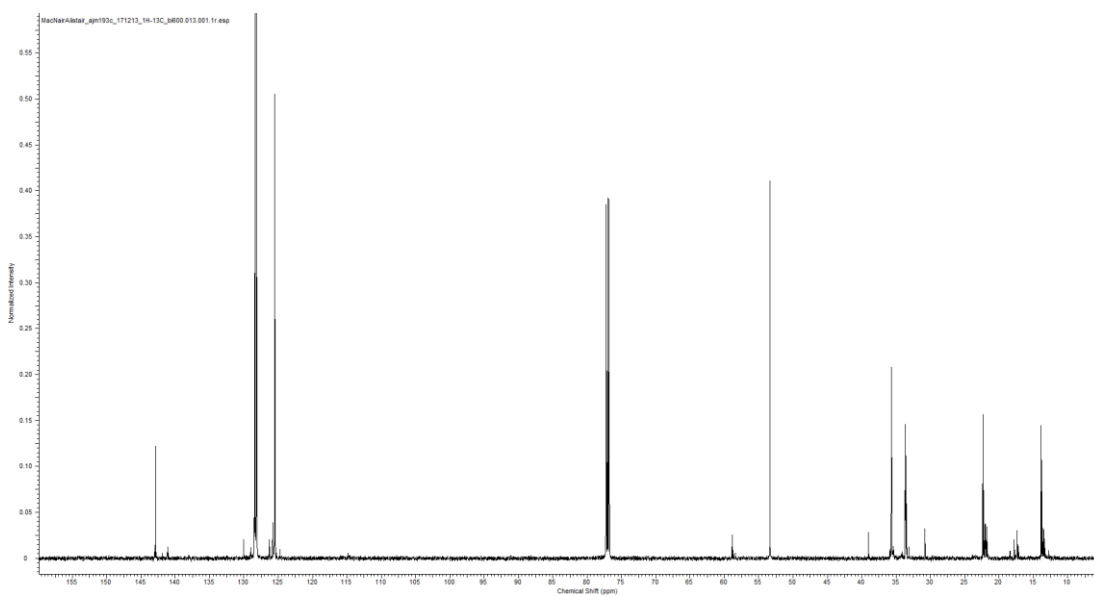
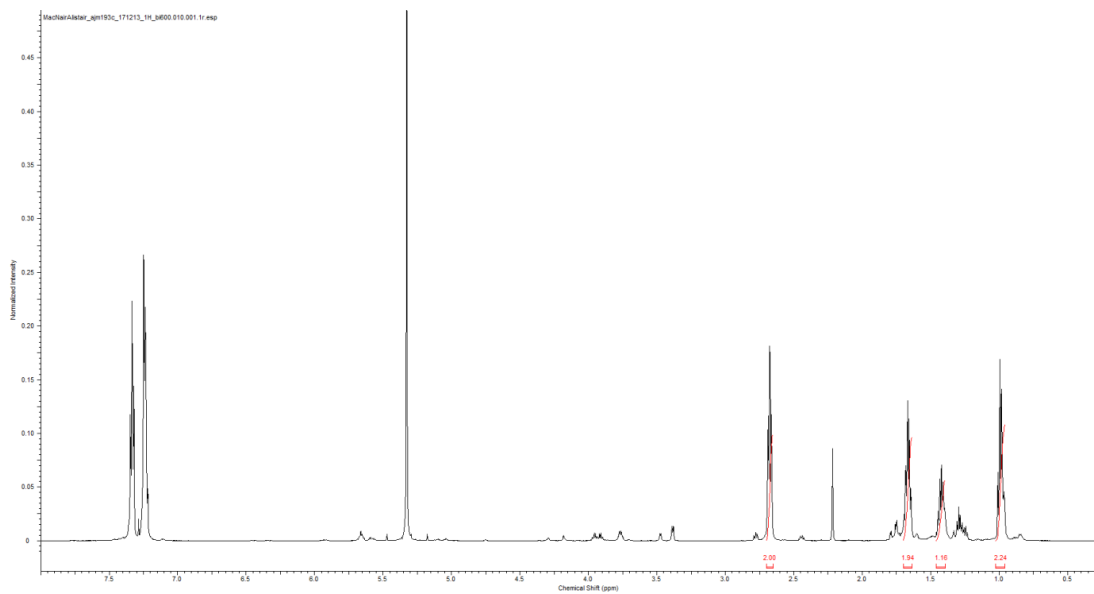
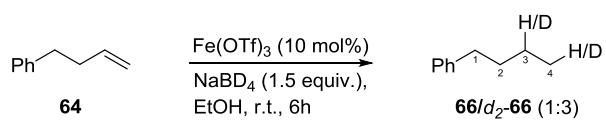
$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 174.0 (C), 79.9 (C), 28.8 ( $\text{CH}_2$ ), 28.1 ( $\text{CH}_3$ ), 9.2 ( $\text{CH}_3$ ).

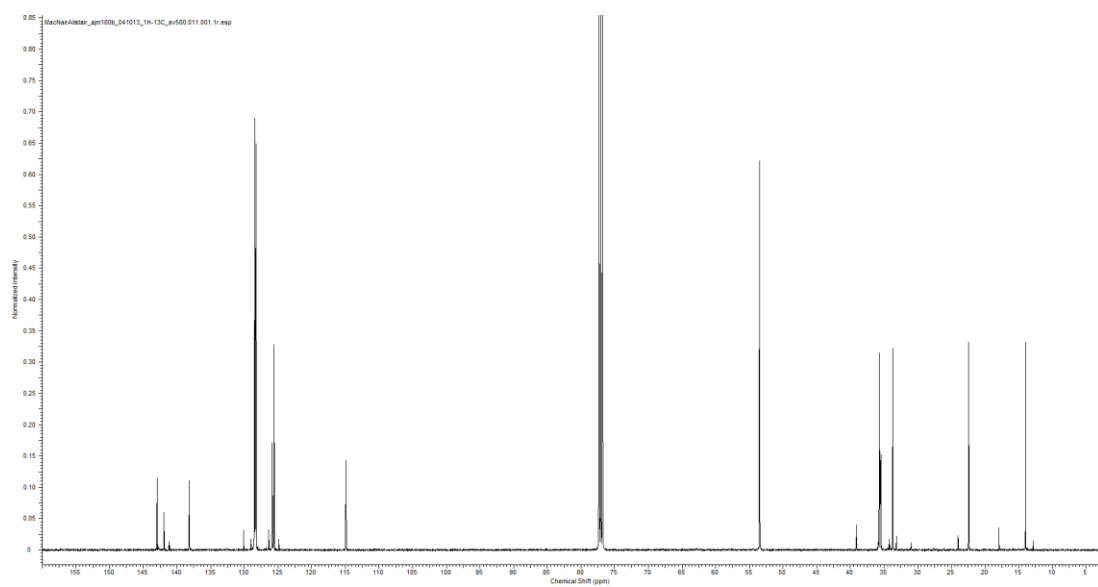
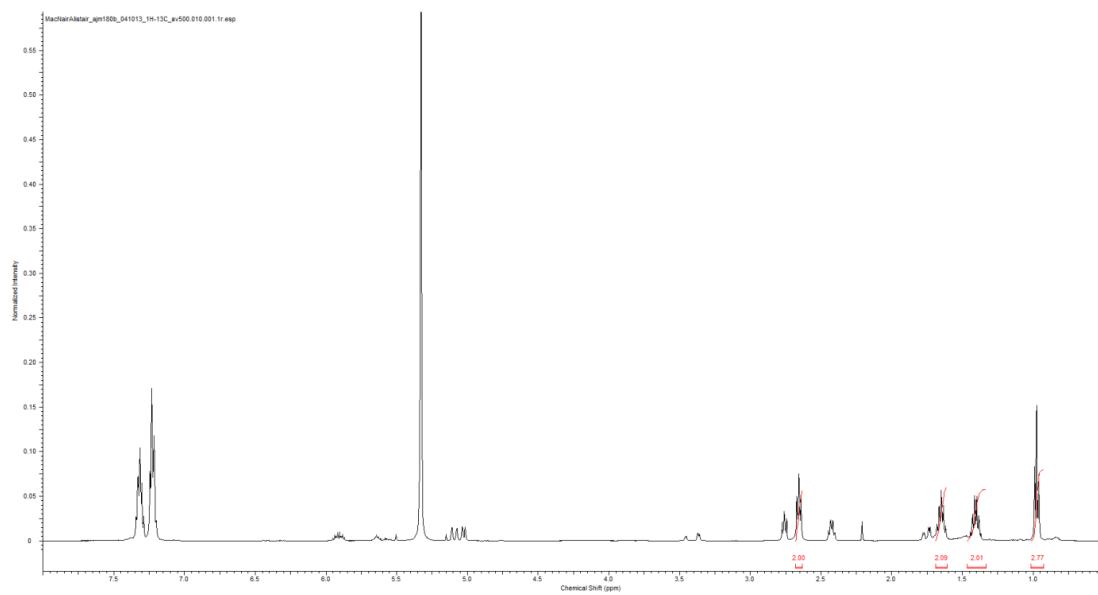
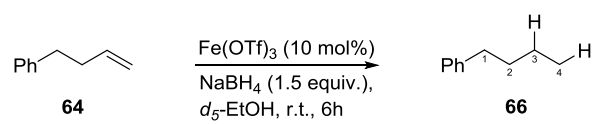
Data were consistent with those of an authentic sample (Aldrich Cat. No. 254525).



## 5.5 ALKENE HYDROGENATION WITH $\text{NaBH}_4$ : DEUTERIUM LABELLING EXPERIMENTS







## 5.6 NITRO GROUP HYDROGENATION REACTIONS WITH $\text{NaBH}_4$ : REACTION OPTIMISATION

### General procedure D:

Anhydrous ethanol (4 mL) was added to a mixture of sodium borohydride (0.379 g, 10.00 mmol, 20.00 equivalents), iron(III) triflate (0.025 g, 0.05 mmol, 0.10 equivalents) and a nitroarene (0.50 mmol, 1.00 equivalent) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 4 hours the reaction mixture was diluted with a saturated solution of sodium hydrogen carbonate (10 mL) and the aqueous phase extracted with dichloromethane ( $3 \times 10$  mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (0.0168 g, 0.10 mmol, 0.20 equivalents) was added as an internal standard, and the crude reaction mixture was analysed by  $^1\text{H}$  NMR spectroscopy.

## 5.7 NITRO GROUP HYDROGENATION WITH $\text{NaBH}_4$ : ISOLATED PRODUCTS

Products were isolated either by flash column chromatography or one of the following methods:

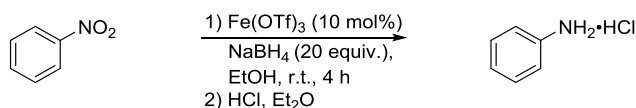
### General procedure E (acid/base extraction):

The crude reaction mixture was diluted with dichloromethane (10 mL), extracted three times with aqueous hydrochloric acid (4 M, 10 mL), the aqueous phase was treated with aqueous sodium hydroxide (6 M) until basic. The aqueous phase was then extracted with dichloromethane ( $3 \times 10$  mL), and the combined organic extracts washed with brine (20 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give the isolated arylamine.

### General procedure F (isolation as hydrochloride salt):

The crude reaction mixture was diluted with diethyl ether (2 mL) and hydrochloric acid (2 M in diethyl ether, 0.25 mL, 0.5 mmol, 1.00 equivalent) was added. The mixture was filtered to give the isolated arylamine as a salt with hydrochloric acid.

### Aniline hydrochloride (141)



According to general procedure **D**, nitrobenzene (0.062 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in

anhydrous ethanol (4 mL). Following purification by general procedure **F**, aniline hydrochloride was isolated as an amorphous grey powder (0.052 g, 0.40 mmol, 80%).

m.p.: 199 °C (diethyl ether).

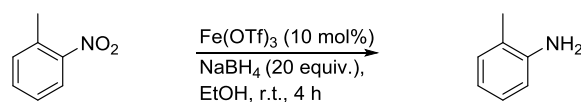
$\nu_{\text{max}}$  (cm<sup>-1</sup>): 3360, 2808, 2594, 2358, 2011, 1600, 1490, 738, 684.

$\delta_{\text{H}}$  (500 MHz, CD<sub>3</sub>OD) 7.55 (app. t,  $J$  = 8.4 Hz, 2H, ArH), 7.50 (t,  $J$  = 7.4 Hz, 1H, ArH), 7.41 (d,  $J$  = 7.0 Hz, 2H, ArH).

$\delta_{\text{C}}$  (500 MHz, CD<sub>3</sub>OD) 132.1 (C), 131.5 (CH), 130.5 (CH), 124.2 (CH).

Data was in accordance with that previously reported.<sup>326</sup>

## 2-Aminotoluene (142)



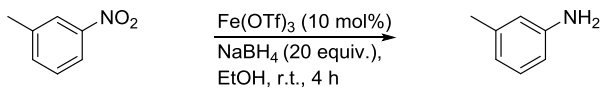
Anhydrous ethanol (4 mL) was added to a mixture of sodium borohydride (0.379 g, 10.0 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and 2-nitrotoluene (0.069 g, 0.059 mL, 0.50 mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 4 h the reaction mixture was diluted with a saturated solution of sodium hydrogen carbonate (10 mL) and the aqueous phase extracted with dichloromethane ( $3 \times 10$  mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. 1,2-Dichloroethane (0.049 g, 0.039 mL, 0.10 mmol) was added as an internal standard, and the crude reaction mixture was analysed by <sup>1</sup>H NMR spectroscopy. Following removal of the internal standard *in vacuo*, 2-aminotoluene was isolated as a dark brown oil (0.043 g, 0.40 mmol, 80%).

$\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 7.11-7.04 (br. m, 2H, ArH), 6.74 (t,  $J$  = 7.5 Hz, 1H, ArH), 6.71 (d,  $J$  = 7.8 Hz, 1H, ArH), 3.30 (br. s, 2H, NH<sub>2</sub>), 2.21 (s, 3H, ArCH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 144.5 (C), 130.5 (CH), 127.0 (CH), 122.4 (C), 118.7 (CH), 115.0 (CH), 17.4 (CH<sub>3</sub>).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 185426).

### 3-Aminotoluene (143)



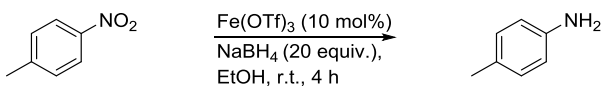
According to general procedure **D**, 3-nitrotoluene (0.069 g, 0.059 mL, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 3-aminotoluene was isolated as a light brown oil (0.026 g, 0.25 mmol, 49%).

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.05 (app. t,  $J = 7.7$  Hz, 1H, ArH), 6.59 (d,  $J = 7.5$  Hz, 1H, ArH), 6.55–6.49 (br. m, 2H, ArH), 3.60 (br. s, 2H,  $\text{NH}_2$ ), 2.28 (s, 3H, ArCH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 146.3 (C), 139.1 (C), 129.1 (CH), 119.4 (CH), 115.9 (CH), 112.2 (CH), 21.4 (CH<sub>3</sub>).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 511218).

### 4-Aminotoluene (144)



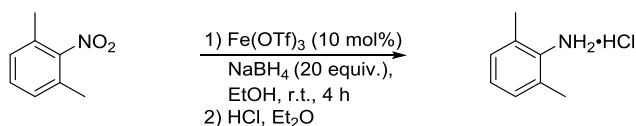
According to general procedure **D**, 4-nitrotoluene (0.069 g, 0.05 mL, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 4-aminotoluene was isolated (0.035 g, 0.33 mmol, 66%).

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.00 (d,  $J = 8.1$ , 2H, ArH), 6.65 (d,  $J = 8.3$ , 2H, ArH), 3.25 (br. s, 2H,  $\text{NH}_2$ ), 2.20 (s, 2H, ArCH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 129.7 (CH), 127.9 (C), 115.5 (CH), 20.4 (CH<sub>3</sub>).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 236314).

## 2,6-Dimethylaniline hydrochloride (145)<sup>476</sup>



According to general procedure **D**, 1,3-dimethyl-2-nitrobenzene (0.076 g, 0.068 mmol, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **F**, 2,6-dimethylaniline hydrochloride was isolated (0.047 g, 0.30 mmol, 59%).

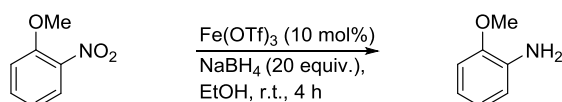
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2816, 2639, 2361, 2012, 1584, 1530, 1464, 1179, 762, 687.

$\delta_{\text{H}}$  (400 MHz,  $\text{CD}_3\text{OD}$ ) 7.30-7.26 (m, 1H, ArH), 7.24-7.21 (m, 2H, ArH), 2.44 (s, 6H, ArCH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CD}_3\text{OD}$ ) 131.4 (C), 129.3 (CH), 128.5 (CH), 128.0 (C), 16.2 (CH<sub>3</sub>).

Data was in accordance with that previously reported.<sup>476</sup>

## 2-Methoxyaniline (146)<sup>326</sup>



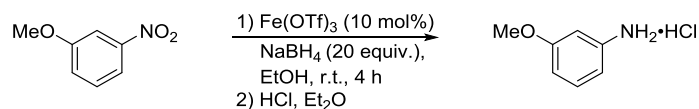
According to general procedure **D**, 2-nitroanisole (0.077 g, 0.061 mmol, 0.50 mmol), iron(III) triflate (0.0252 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 2-methoxyaniline was isolated as a colourless oil (0.046 g, 0.37 mmol, 75%).

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 6.89-6.75 (m, 4H, ArH), 3.90 (s, 3H, OCH<sub>3</sub>), 3.74 (br s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 147.2 (C), 136.1 (C), 121.0 (CH), 118.4 (CH), 114.9 (CH), 110.3 (CH), 55.3 (CH<sub>3</sub>).

Data was in accordance with that previously reported.<sup>326</sup>

### 3-Methoxyaniline hydrochloride (147)<sup>476</sup>



According to general procedure **D**, 3-nitroanisole (0.077 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **F**, 3-methoxyaniline hydrochloride was isolated as an amorphous brown powder (0.054 g, 0.34 mmol, 68%).

m.p.: 167-168 °C (diethylether).

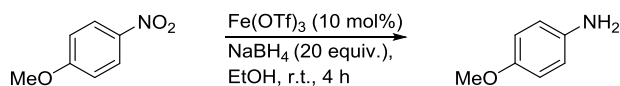
$\nu_{\text{max}}$  (cm<sup>-1</sup>): 2940, 2600, 2359, 1578, 1539, 1466, 1423, 1319, 1252, 1159, 1038

$\delta_{\text{H}}$  (400 MHz, CD<sub>3</sub>OD) 7.45 (m, 1H, ArH), 7.06 (dd,  $J$  = 8.4, 2.4 Hz, 1H, ArH), 6.95 (dd,  $J$  = 7.8, 2.1 Hz, 1H, ArH), 6.93 (m, 1H, ArH), 3.85 (s, 3H, OCH<sub>3</sub>).

$\delta_{\text{C}}$  (100 MHz, CD<sub>3</sub>OD) 162.5 (C), 133.1 (C), 132.4 (CH), 116.1 (CH), 115.7 (CH), 110.3 (CH), 56.3 (CH<sub>3</sub>).

Data was in accordance with that previously reported.<sup>476</sup>

### 4-Methoxyaniline (148)<sup>476</sup>



According to general procedure **D**, 4-nitroanisole (0.077 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 4-methoxyaniline was isolated as a colourless oil (0.015 g, 0.12 mmol, 24%).

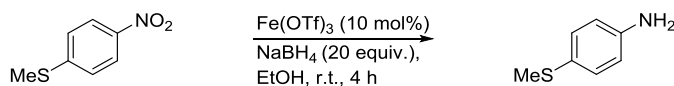
$\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 6.76 (dt,  $J$  = 9.0, 2.3 Hz, 2H, ArH), 6.66 (d,  $J$  = 9.0, 2.4 Hz, 2H, ArH), 3.76 (s, 3H, OCH<sub>3</sub>), 3.32 (br. s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>) 152.7 (C), 139.9 (C), 116.4 (CH), 114.8 (CH), 55.9 (CH<sub>3</sub>).

Data was in accordance with that previously reported.<sup>476</sup>



#### 4-Methylsulfanylaniline (149)<sup>476</sup>



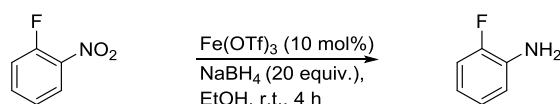
According to general procedure **D**, 4-nitrothioanisole (0.169 g, 1.00 mmol), iron(III) triflate (0.050 g, 0.10 mmol) and sodium borohydride (0.757 g, 20.0 mmol) were reacted in anhydrous ethanol (8 mL). Following purification by general procedure **E**, 4-(methyl)-aniline was isolated as an amorphous orange solid (0.103 g, 0.76 mmol, 76 %).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.21 (dt,  $J = 8.7, 2.1$  Hz, 2H, ArH), 6.66 (dt,  $J = 8.7, 2.1$  Hz, 2H, ArH), 3.67 (br. s, 2H,  $\text{NH}_2$ ), 2.44 (s, 3H,  $\text{SCH}_3$ ).

$\delta_{\text{C}}$  (150 MHz,  $\text{CDCl}_3$ ) 145.1 (C), 131.1 (CH), 125.8 (C), 115.7 (CH), 18.8 ( $\text{CH}_3$ ).

Data was in accordance with that previously reported.<sup>476</sup>

#### 2-Fluoroaniline (151)

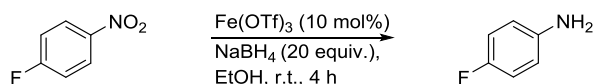


According to general procedure **D**, 1-fluoro-2-nitrobenzene (0.053 mL, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL) to give 2-Fluoroaniline (73% by  $^1\text{H}$  NMR spectroscopy). Product was not successfully isolated.

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.04-6.92 (m, 2H, ArH), 6.82-6.77 (m, 1H, ArH), 6.75-6.68 (m, 1H, ArH), 3.56 (br. s, 2H,  $\text{NH}_2$ ).

Data were consistent with those of an authentic sample (Aldrich Cat. No. F3401).

#### 4-Fluoroaniline (152)

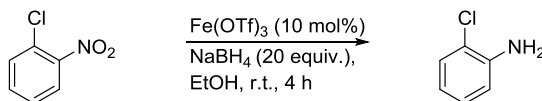


According to general procedure **D**, 4-fluoro-1-nitrobenzene (0.070 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Product was not successfully isolated.

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 6.91-6.84 (m, 2H, ArH), 6.66-6.60 (m, 2H, ArH), 3.46 (br. s, 2H,  $\text{NH}_2$ ).

Data were consistent with those of an authentic sample (Aldrich Cat. No. F3800).

#### 2-Chloroaniline (153)



According to general procedure **D**, 1-chloro-2-nitrobenzene (0.064 g, 0.058 mL, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 2-chloroaniline was isolated as brown needles (0.011 g, 0.09 mmol, 17%).

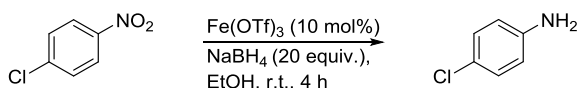
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2835, 2590, 2139, 1988, 1562, 1514, 1477, 1444, 1400, 1159, 1097, 1051, 754, 680.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.26 (m, 1H, ArH), 7.09 (m, 1H, ArH), 6.79 (m, 1H, ArH), 6.71 (m, 1H, ArH), 4.06 (br. s, 2H,  $\text{NH}_2$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 142.9 (C), 129.4 (CH), 127.6 (CH), 119.3 (C), 119.1 (CH), 115.9 (CH).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 23310).

#### 4-Chloroaniline (154)



According to general procedure **D**, 1-chloro-4-nitrobenzene (0.079 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 4-chloroaniline was isolated as a brown plates (0.030 g, 0.24 mmol, 47%).

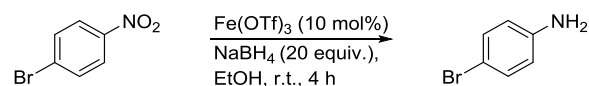
$\nu_{\max}$  (cm<sup>-1</sup>): 3474, 3383, 2359, 2342, 1614, 1499, 1288, 1180, 1090, 829, 640.

$\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.11 (dt,  $J$  = 8.8, 2.2 Hz, 2H, ArH), 6.62 (dt,  $J$  = 8.8 Hz, 2.1 Hz, 2H, ArH), 3.62 (br. s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 144.9 (C), 129.1 (CH), 123.2 (C), 116.2 (CH).

Data were consistent with those of an authentic sample (Aldrich Cat. No. C22415).

#### 4-Bromoaniline (155)



According to general procedure **D**, 1-bromo-4-nitrobenzene (0.101 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following flash column chromatography (conditions: silica 15 g; 30 mm Ø; dichloromethane/methanol, 95:5 v/v) 4-bromoaniline was isolated as an orange amorphous solid (0.087 g, 0.51 mmol, 51%).

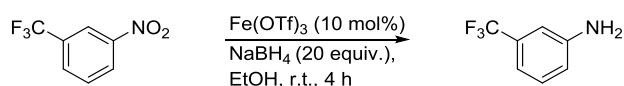
$\nu_{\max}$  (cm<sup>-1</sup>): 3471, 3381, 1610, 1593, 1487, 1284, 1180, 1151, 1068, 815.

$\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.26 (dt,  $J$  = 8.9, 2.3 Hz, 2H, ArH), 6.58 (dt,  $J$  = 8.9 Hz, 2.3 Hz, 2H, ArH) 3.67 (br. s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (150 MHz, CDCl<sub>3</sub>) 148.1 (C), 134.7 (CH), 119.4 (CH), 112.9 (C).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 100900).

#### 3-(Trifluoromethyl)aniline (156)<sup>477</sup>



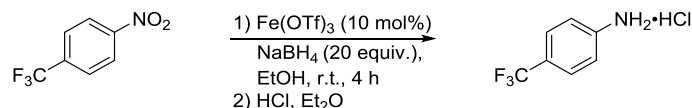
According to general procedure **D**, 3-nitrobenzotrifluoride (0.067 mL, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **E**, 3-(trifluoromethyl)aniline was isolated as a yellow oil (0.044 g, 0.27 mmol, 55%).

$\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.27 (t,  $J$  = 7.8 Hz, 1H, ArH), 7.02 (dt,  $J$  = 7.7, 0.7 Hz, 1H, ArH), 6.92 (s, 1H, ArH), 6.84 (dd,  $J$  = 8.0, 2.3 Hz, 1H, ArH), 3.86 (br. s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 146.7 (C), 131.6 (q,  $J = 31.9$  Hz, C), 129.7 (CH), 124.2 (q,  $J = 272.2$  Hz,  $\text{CF}_3$ ), 118.0 (CH), 115.0 (q,  $J = 4.0$  Hz, CH), 111.3 (q,  $J = 4.0$  Hz, CH).

Data was in accordance with that previously reported.<sup>477</sup>

#### 4-(Trifluoromethyl)aniline hydrochloride (157)<sup>477</sup>



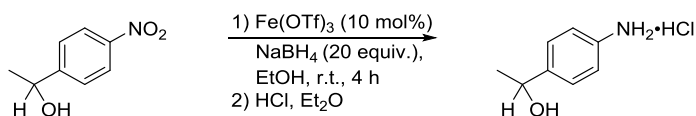
According to general procedure **D**, 4-nitrobenzotrifluoride (0.096 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **F**, 4-(trifluoromethyl)aniline was isolated as an amorphous cream solid (0.075 g, 0.38 mmol, 76%).

$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2849, 2590, 2359, 1616, 1510, 1321, 1194, 1161, 1126, 1065, 1016, 827.

$\delta_{\text{H}}$  (400 MHz,  $\text{CD}_3\text{OD}$ ) 7.83 (d,  $J = 8.4$ , 2H, ArH), 7.52 (d,  $J = 8.4$ , 2H, ArH).

Data was in accordance with that previously reported.<sup>477</sup>

#### 1-(4-Aminophenyl)ethanol hydrochloride (158)<sup>478</sup>



According to general procedure **D**, 1-(4-nitrophenyl)ethanone (0.083 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **F**, 1-(4-aminophenyl)ethanol hydrochloride was isolated (0.013 g, 0.08 mmol, 15%).

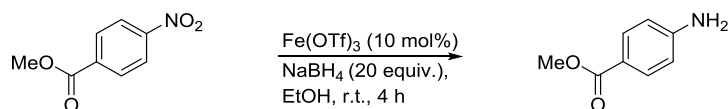
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3383, 2577, 2455, 2361, 2342, 1578, 1514, 1420, 1206, 1067, 827.

$\delta_{\text{H}}$  (400 MHz,  $\text{CD}_3\text{OD}$ ) 7.50 (d,  $J = 8.4$  Hz, 2H, ArH), 7.39 (d,  $J = 8.6$  Hz, 2H, ArH), 4.41 (q,  $J = 6.5$  Hz, 1H, ArCH), 1.40 (d,  $J = 6.5$  Hz, 3H,  $\text{CHCH}_3$ ).

$\delta_{\text{C}}$  (100 MHz,  $\text{CD}_3\text{OD}$ ) 146.7 (C), 131.1 (C), 129.2 (CH), 124.4 (CH), 80.1 (CH), 24.1 ( $\text{CH}_3$ ).

Data was in accordance with that previously reported.<sup>478</sup>

### Methyl 4-aminobenzoate (159)



According to general procedure **D**, methyl 4-nitrobenzoate (0.181 g, 1.00 mmol), iron(III) triflate (0.050 g, 0.10 mmol) and sodium borohydride (0.757 g, 20.0 mmol) were reacted in anhydrous ethanol (8 mL). Following purification by general procedure **E**, methyl 4-aminobenzoate was isolated as an amorphous yellow solid (0.121 g, 0.80 mmol, 80%).

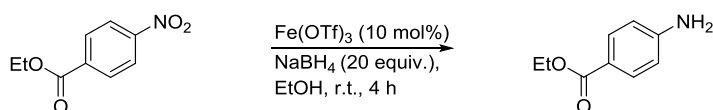
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3339, 1682, 1597, 1275, 1173, 1111.

$\delta_{\text{H}}$  (400 MHz:  $\text{CDCl}_3$ ) 7.86 (dt,  $J = 8.6, 1.8$  Hz, 2H, ArH), 6.66 (dt,  $J = 8.7, 1.9$  Hz, 2H, ArH), 3.86 (s, 3H,  $\text{OCH}_3$ ).

$\delta_{\text{C}}$  (150 MHz:  $\text{CDCl}_3$ ) 167.1 (C), 150.8 (C), 131.6 (CH), 119.8 (C), 113.8 (CH), 51.6 ( $\text{CH}_3$ ).

Data were consistent with those of an authentic sample (Aldrich Cat. No.274186).

### Ethyl 4-aminobenzoate (160)<sup>478</sup>



According to general procedure **D**, ethyl 4-nitrobenzoate (0.181 g, 1.00 mmol), iron(III) triflate (0.050 g, 0.10 mmol) and sodium borohydride (0.757 g, 20.0 mmol) were reacted in anhydrous ethanol (8 mL). Following purification by general procedure **E**, ethyl 4-aminobenzoate was isolated as an amorphous yellow solid (0.046 g, 0.28 mmol, 28%).

m.p.: 87 to 88 °C (dichloromethane).

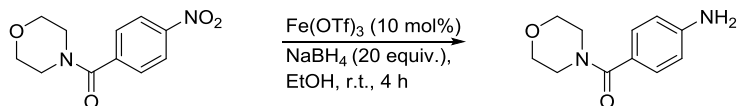
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3341, 1680, 1595, 1275, 1171, 1109.

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.85 (dt,  $J = 8.7, 1.9$  Hz, 2H, ArH), 6.63 (dt,  $J = 8.7, 1.9$  Hz, 2H, ArH), 4.31 (q,  $J = 7.2$  Hz, 2H,  $\text{OCH}_2$ ), 4.07 (s, 2H,  $\text{NH}_2$ ), 1.37 (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_3$ ).

$\delta_{\text{C}}$  (150 MHz,  $\text{CDCl}_3$ ) 166.7 (C), 150.7 (C), 131.5 (CH), 120.1 (C), 113.7 (CH), 60.3 ( $\text{CH}_2$ ), 14.4 ( $\text{CH}_3$ ).

Data was in accordance with that previously reported.<sup>478</sup>

#### 4-(4-Aminobenzoyl)morpholine (161)<sup>479</sup>



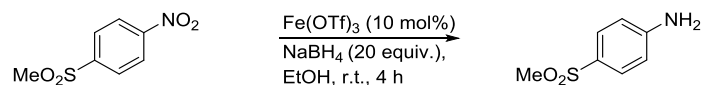
According to general procedure **D**, 4-(4-nitrobenzoyl)morpholine (0.130 g, 0.55 mmol), iron(III) triflate (0.028 g, 0.05 mmol) and sodium borohydride (0.416 g, 11.0 mmol) were reacted in anhydrous ethanol (4.25 mL). Following purification by general procedure **E**, 4-(4-aminobenzoyl)morpholine was isolated as a pale brown amorphous solid (0.067 g, 0.32 mmol, 32%).

$\delta_{\text{H}}$  (600 MHz: CDCl<sub>3</sub>) 7.29 (d,  $J$  = 8.3 Hz, 2H, ArH), 6.68 (d,  $J$  = 8.3 Hz, 2H, ArH), 3.89 (br. s, 2H, NH<sub>2</sub>), 3.72 (br. s, 4H, CH<sub>2</sub>), 3.67 (br. s, 4H, CH<sub>2</sub>).

$\delta_{\text{C}}$  (150 MHz: CDCl<sub>3</sub>) 170.9 (C), 148.3 (C), 129.4 (CH), 124.7 (C), 114.2 (CH), 67.0 (CH<sub>2</sub>), 65.8 (CH<sub>2</sub>).

Data was in accordance with that previously reported.<sup>479</sup>

#### 4-(Methylsulfonyl)-aniline (162)<sup>476</sup>



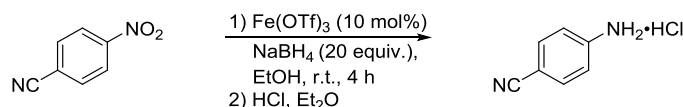
According to general procedure **D**, 4-nitrothioanisole (0.123 g, 1.00 mmol), iron(III) triflate (0.050 g, 0.10 mmol) and sodium borohydride (0.757 g, 20.0 mmol) were reacted in anhydrous ethanol (8 mL). Following purification by general procedure **E**, 4-(methyl)-aniline was isolated as an amorphous orange solid (0.103 g, 0.76 mmol, 76%).

$\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.73 (dt,  $J$  = 8.8, 2.0 Hz, 2H, ArH), 6.74 (dt,  $J$  = 8.8, 2.0 Hz, 2H, ArH), 4.20 (br. s, 2H, NH<sub>2</sub>), 3.03 (s, 3H, SCH<sub>3</sub>).

$\delta_{\text{C}}$  (126 MHz, CDCl<sub>3</sub>) 151.2 (C), 129.5 (CH), 129.0 (C), 114.1 (CH), 45.0 (CH<sub>3</sub>).

Data was in accordance with that previously reported.<sup>476</sup>

#### 4-Aminobenzonitrile hydrochloride (**163**)<sup>476</sup>



According to general procedure **D**, 4-nitrobenzonitrile (0.074 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following purification by general procedure **C**, 4-aminobenzonitrile hydrochloride was isolated as an amorphous dark yellow solid (0.060 g, 0.39 mmol, 77%).

m.p.: 200-202 °C (diethylether).

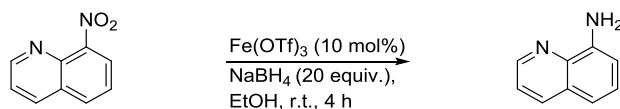
$\nu_{\max}$  (cm<sup>-1</sup>): 2808, 2577, 2361, 2236, 2102, 1609, 1503, 1371, 835, 812.

$\delta_{\text{H}}$  (400 MHz, CD<sub>3</sub>OD) 7.77 (d,  $J$  = 8.8 Hz, 2H, ArH), 7.31 (d,  $J$  = 8.8 Hz, 2H, ArH).

$\delta_{\text{C}}$  (100 MHz, CD<sub>3</sub>OD) 142.1 (C), 135.3 (CH), 122.5 (CH), 119.5 (C), 109.7 (C).

Data was in accordance with that previously reported.<sup>476</sup>

#### 8-Aminoquinoline (**164**)



According to general procedure **D**, 8-nitroquinoline (0.0871 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). The reaction mixture was diluted with water (5 mL) then treated with sodium cyanide (0.015 g, 0.30 mmol). The resultant aqueous phase was extracted with EtOAc (3 × 10 mL) then concentrated in vacuo. Following flash column chromatography (conditions: silica 15 g, 30 mm Ø; petroleum spirit/ethyl acetate, 9:1 v/v) 8-aminoquinoline was isolated as a brown plates (0.037 g, 0.25 mmol, 51%).

m.p.: 57-60 °C (petroleum spirit/ethyl acetate, 9:1 v/v).

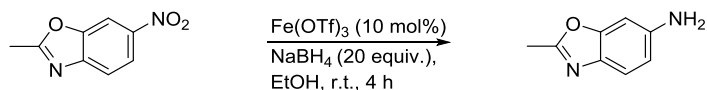
$\nu_{\max}$  (cm<sup>-1</sup>): 3451, 3348, 3034, 2924, 2359, 1591, 1504, 1368, 1094, 818, 789, 760.

$\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>) 8.77 (dd,  $J$  = 4.1, 1.7 Hz, 1H, ArH), 8.08 (dd,  $J$  = 8.3, 1.7 Hz, 1H, ArH), 7.40-7.32 (m, 2H, ArH), 7.16 (dd,  $J$  = 8.1, 1.2 Hz, 1H, ArH), 6.94 (dd,  $J$  = 7.5, 1.3 Hz, 1H, ArH), 4.99 (br. s, 2H, NH<sub>2</sub>).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 147.5 (CH), 144.0 (C), 138.5 (C), 136.0 (CH), 128.9 (C), 127.4 (CH), 121.4 (CH), 116.1 (CH), 110.1 (CH).

Data were consistent with those of an authentic sample (Aldrich Cat. No. 260789).

### 2-Methyl-6-benzoxazolamine (165)<sup>480</sup>



According to general procedure **D**, 2-methyl-6-nitrobenzoxazole (0.089 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.0 mmol) were reacted in anhydrous ethanol (4 mL). Following flash column chromatography (conditions: silica 15 g, 30 mm Ø; hexane/ethyl acetate 7:3 v/v) 2-methyl-6-benzoxazolamine was isolated as brown prisms (0.018 g, 0.12 mmol, 24%).

m.p.: 133-137 °C (hexane/ethyl acetate, 70:30, v/v).

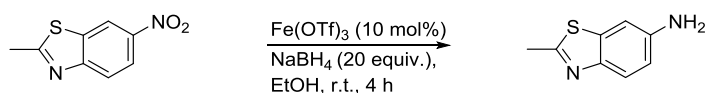
$\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3362, 3213, 2359, 2342, 1614, 1576, 1493, 1435, 818, 557.

$\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.40 (d,  $J = 8.4$  Hz, 1H, ArH), 6.78 (d,  $J = 1.9$  Hz, 1H, ArH), 6.65 (dd,  $J = 8.4, 2.2$  Hz, 1H, ArH), 2.57 (s, 3H,  $\text{CH}_3$ ).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 161.7 (C), 152.2 (C), 144.3 (C), 134.0 (C), 119.5 (CH), 112.5 (CH), 96.5 (CH), 14.4 ( $\text{CH}_3$ ).

Data was in accordance with that previously reported.<sup>480</sup>

### 2-Methyl-6-benzothiazolamine (166)<sup>481</sup>



According to general procedure **D**, 2-methyl-6-nitro-benzothiazole (0.097 g, 0.50 mmol), iron(III) triflate (0.025 g, 0.05 mmol) and sodium borohydride (0.378 g, 10.00 mmol) were reacted in anhydrous ethanol (4 mL). Following flash column chromatography (conditions: silica 15 g, 30 mm Ø; hexane/ethyl acetate, 1:1 v/v) 2-methyl-6-benzothiazolamine was isolated as an amorphous pale yellow solid (0.046 g, 0.28 mmol, 56%).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.72 (d,  $J = 8.7$  Hz, 1H, ArH), 7.06 (d,  $J = 2.2$  Hz, 1H, ArH), 6.80 (dd,  $J = 8.6, 2.3$  Hz, 1H, ArH), 3.80 (br. s, 2H,  $\text{NH}_2$ ), 2.76 (s, 3H,  $\text{CH}_3$ ).

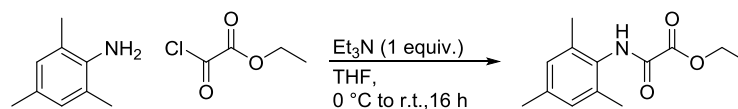


$\delta_{\text{C}}$  (500 MHz,  $\text{CDCl}_3$ ) 162.6 (C), 146.7 (C), 144.0 (C), 137.2 (C), 122.7 (CH), 155.1 (CH), 105.8 (CH), 19.8 ( $\text{CH}_3$ ).

Data was in accordance with that previously reported.<sup>481</sup>

## 5.8 IMIDAZOLIUM SALT SYNTHESIS

### *N*-(2,4,6-Trimethylphenyl)-oxalamic acid, ethyl ester (231)<sup>456,457</sup>



Ethyl chlorooxoacetate (2.73 g, 20.0 mmol) was added dropwise to a solution of 2,4,6-trimethylaniline (2.70 g, 20.0 mmol) and triethylamine (2.02 g, 20.0 mmol) in anhydrous tetrahydrofuran (20 mL) under a nitrogen atmosphere at 0 °C. The resulting solution was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (10 mL) washed with aqueous hydrochloric acid (1.0 M,  $2 \times 10$  mL), saturated sodium hydrogen carbonate ( $2 \times 10$  mL) and brine (10 mL), the organic phase was dried over magnesium sulfate and concentrated *in vacuo*. Following recrystallisation from a mixture of hexane and ethyl acetate (9:1 v/v), *N*-(2,4,6-trimethylphenyl)-oxalamic acid, ethyl ester (3.75 g, 15.9 mmol, 78%) was isolated as colourless needles.

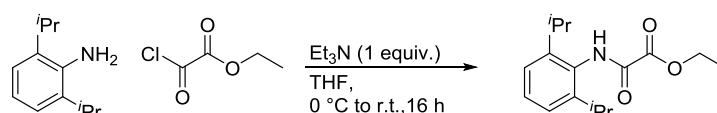
m.p.: 77-80 °C (hexane/ethyl acetate).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 8.36 (s, 1H, NH), 6.95 (s, 2H, ArH), 4.46 (q,  $J = 7.2$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 2.31 (s, 3H, *p*- $\text{CH}_3$ ), 2.23 (s, 6H, *o*- $\text{CH}_3$ ), 1.48 (t,  $J = 7.2$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 161.0 (C), 154.7 (C), 137.7 (C), 134.7 (C), 129.5 (C), 129.1 (CH), 63.6 ( $\text{CH}_2$ ), 20.9 ( $\text{CH}_3$ ), 18.3 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ).<sup>479</sup>

Data were in accordance with that previously reported.<sup>456,457</sup>

### Oxanilic acid, 2',6'-diisopropyl-, ethyl ester (232)<sup>456,457</sup>



Ethyl chlorooxoacetate (6.83 g, 50.0 mmol) was added dropwise to a solution of 2, 6-diisopropylaniline (8.87 g, 50.0 mmol) and triethylamine (5.06 g, 50.0 mmol) in anhydrous tetrahydrofuran (50 mL) under a nitrogen atmosphere at 0 °C. The resulting solution was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (25 mL)

washed with aqueous hydrochloric acid (1.0 M, 2 × 25 mL), saturated sodium hydrogen carbonate (2 × 25 mL) and brine (25 mL), the organic phase was dried over magnesium sulfate and concentrated *in vacuo*. Following recrystallisation from a mixture of hexane and ethyl acetate (9:1), oxanilic acid, 2', 6'-diisopropyl-, ethyl ester was isolated as colourless needles (9.48 g, 34.2 mmol, 68 %).

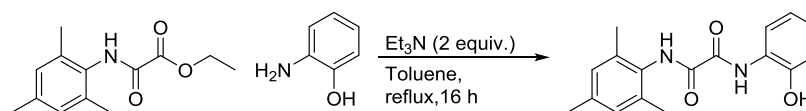
$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 3269, 2961, 1736, 1686, 1501, 1458, 1281, 1206, 1159, 1018, 731.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 8.38 (br. s, 1H, NH), 7.37 (t,  $J = 7.7$  Hz, 1H, ArH), 7.23 (d,  $J = 7.7$  Hz, 2H, ArH), 4.48 (q,  $J = 7.2$  Hz, 2H,  $\text{CH}_2$ ), 3.04 (sep.,  $J = 6.9$  Hz, 2H, CH), 1.49 (t,  $J = 7.2$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 1.24 (d,  $J = 6.9$  Hz, 12H,  $\text{CH}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 161.1 (C), 155.9 (C), 145.9 (C), 129.4 (C), 129.0 (CH), 123.8 (CH), 63.7 ( $\text{CH}_2$ ), 28.9 (CH), 23.7 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ).

Data were in accordance with that previously reported.<sup>456,457</sup>

**Ethanediamide, *N*-(2-hydroxyphenyl)-*N'*-(2,4,6-trimethylphenyl)- (233)**<sup>456,457</sup>



Triethylamine (6.07 g, 60.0 mmol) was added to a suspension of *N*-(2,4,6-trimethylphenyl)-oxalamic acid, ethyl ester (7.06 g, 30.0 mmol) and 2-aminophenol (3.27 g, 30.0 mmol) in toluene (60 mL). The suspension was heated, dissolving any remaining solids, then stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate such that any solids were dissolved. The solution was washed with aqueous hydrochloric acid (1.0 M, 2 × 50 mL), the aqueous phase was extracted with ethyl acetate (2 × 50 mL) and the combined organic phase were washed with brine (100 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an amorphous yellow solid. Following recrystallisation from toluene *N*-(2-hydroxyphenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (6.10 g, 20.5 mmol, 68%) was recovered as colourless blocks.

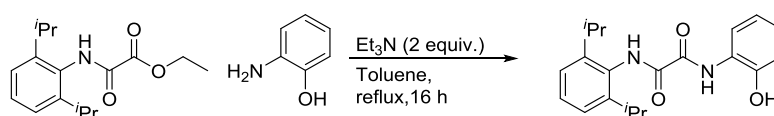
m.p.: 196-197 °C (toluene).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 9.61 (s, 1H, OH), 8.77 (s, 1H, NH), 8.05 (s, 1H, NH), 7.40-7.36 (m, 1H, ArH), 7.25-7.20 (m, 1H, ArH), 7.09-7.05 (m, 1H, ArH), 7.00-6.95 (m, 3H, ArH), 2.31 (s, 3H, *p*- $\text{CH}_3$ ), 2.24 (s, 6H, *o*- $\text{CH}_3$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 158.1 (C), 157.4 (C), 148.2 (C), 138.0 (C), 134.7 (C), 129.3 (C), 129.2 (CH), 127.8 (CH), 124.0 (C), 122.2 (CH), 120.9 (CH), 119.1 (CH), 21.0 ( $\text{CH}_3$ ), 18.3 ( $\text{CH}_3$ ).

Data were in accordance with that previously reported.<sup>456,457</sup>

### Ethanediamide, *N*-(2-hydroxyphenyl)-*N'*-(2,6-diisopropylphenyl) (234)



Oxanilic acid, 2',6'-diisopropylphenyl-, ethyl ester (8.32 g, 30.0 mmol) and 2-aminophenol (3.27 g, 30.0 mmol) were suspended in toluene (60 mL). Triethylamine (6.07 g, 60.0 mmol) was added to the resulting suspension. The suspension was heated, dissolving any remaining solids, then stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate such that any solids were dissolved. The solution was washed with aqueous hydrochloric acid (1 M,  $2 \times 50$  mL), the aqueous layer was extracted with ethyl acetate ( $2 \times 50$  mL) and the combined organic layers were washed with brine (100 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed *in vacuo* to give an amorphous yellow solid. Following recrystallisation from toluene/ethyl acetate *N*-(2-hydroxyphenyl)-*N'*-(2,6-diisopropylphenyl)-ethanediamide was recovered as an amorphous white powder (3.37 g, 9.90 mmol, 33%).

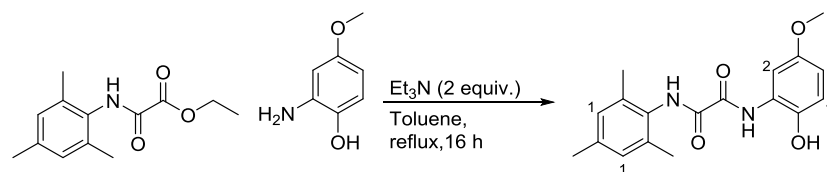
$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 3347, 3252, 2963, 1661, 1599, 1514, 1499, 1456, 1364, 1285, 1103, 746, 729.

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 9.63 (br. s, 1H, OH), 8.83 (br. s, 1H, NH), 7.83 (s, 1H, NH), 7.50 (dd,  $J = 8.0, 1.5$  Hz, 1H, ArH), 7.38 (t,  $J = 7.8$  Hz, 1H, ArH), 7.25 (d,  $J = 7.8$  Hz, 2H, ArH), 7.18 (td,  $J = 7.8, 1.5$  Hz, 1H, ArH), 7.01 (dd,  $J = 8.2, 1.3$  Hz, 1H, ArH), 6.96 (td,  $J = 7.9, 1.3$  Hz, 1H, ArH), 3.04 (sep.,  $J = 6.9$  Hz, 2H,  $\text{CH}(\text{CH}_3)_2$ ), 1.21 (d,  $J = 6.9$  Hz, 12H,  $\text{CH}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 158.7 (C), 158.2 (C), 148.0 (C), 146.1 (C), 129.5 (C), 129.1 (CH), 127.6 (CH), 124.1 (C), 123.8 (CH), 122.2 (CH), 120.9 (CH), 118.8 (CH), 28.9 (CH), 23.4 ( $\text{CH}_3$ ).

Data were in accordance with that previously reported.<sup>456,457</sup>

**Ethanediamide, *N*-(2-hydroxy-, 5-methoxyphenyl)-*N'*-(2,4,6-trimethylphenyl)- (235)**



Triethylamine (4.05 g, 40.0 mmol) was added to a suspension of *N*-(2,4,6-trimethylphenyl)-oxalamide acid, ethyl ester (4.71 g, 20.0 mmol) and 2-amino-4-methoxyphenol (2.78 g, 20.0 mmol) in toluene (40 mL). The suspension was heated, dissolving any remaining solids, then stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate such that any solids were dissolved. The solution was washed with aqueous hydrochloric acid (1.0 M, 2 × 40 mL), the aqueous phase was extracted with ethyl acetate (2 × 40 mL) and the combined organic phase were washed with brine (80 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an amorphous yellow solid. Following recrystallisation from toluene *N*-(2-hydroxy-, 5-methoxyphenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (6.26 g, 19.1 mmol, 95%) was recovered as cream coloured needles.

m.p.: 172-173 °C (toluene).

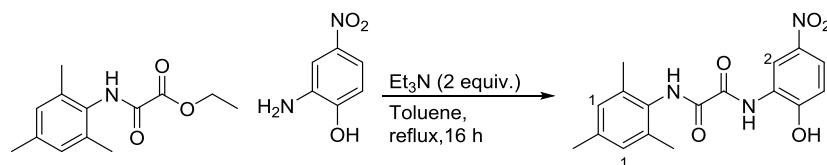
$\nu_{\max}/\text{cm}^{-1}$  (neat): 3368, 3331, 1668, 1611, 1524, 1497, 1433, 1358, 1273, 1204, 1204, 1180, 1157, 1047.

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 9.65 (s, 1H, OH), 8.82 (s, 1H, NH), 7.18 (d,  $J = 2.9$  Hz, 1H, ArH<sup>2</sup>), 7.10 (s, 1H, NH), 7.00 (s, 2H, ArH<sup>1</sup>), 6.96 (d,  $J = 8.9$  Hz, 1H, ArH<sup>4</sup>), 6.78 (dd,  $J = 8.9, 2.9$  Hz, 1H, ArH<sup>3</sup>), 3.81 (s, 3H, OCH<sub>3</sub>), 2.35 (s, 3H, *p*-CH<sub>3</sub>), 2.25 (s, 6H, *o*-CH<sub>3</sub>).

$\delta_{\text{C}}$  (125 MHz,  $\text{CD}_2\text{Cl}_2$ ) 158.8 (C), 158.0 (C), 154.5 (C), 142.2 (C), 138.5 (C), 135.5 (C), 130.2 (C), 129.6 (CH), 125.2 (C), 119.7 (CH), 113.6 (CH), 107.6 (CH), 56.3 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>).

HRMS (EI) Exact mass calculated for  $\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_2$   $[\text{M}]^+$ : 328.14176, found: 328.14126.

**Ethanediamide, *N*-(2-hydroxy-, 5-nitrophenyl)-*N'*-(2,4,6-trimethylphenyl)- (236)**



Triethylamine (5.06 g, 50.0 mmol) was added a suspension of *N*-(2,4,6-trimethylphenyl)-oxalamide acid, ethyl ester (5.88 g, 25.0 mmol) and 2-amino-4-nitrophenol (3.85 g, 25.0 mmol) in

toluene (40 mL). The suspension was heated, dissolving any remaining solids, then stirred under reflux overnight. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate such that any solids were dissolved. The solution was washed with aqueous hydrochloric acid (1.0 M,  $2 \times 40$  mL), the aqueous phase was extracted with ethyl acetate ( $2 \times 40$  mL) and the combined organic phases were washed with brine (80 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an amorphous yellow solid. Following recrystallisation from toluene *N*-(2-hydroxy-, 5-methoxyphenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (2.57 g, 7.20 mmol, 29%) was recovered as cream coloured needles.

m.p.: decomposed when heated above 160 °C (toluene).

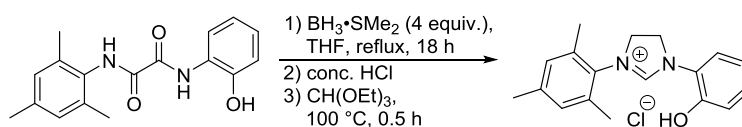
$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 3381, 1668, 1599, 1531, 1493, 1339, 1279, 1227, 1076.

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_3\text{CN}$ ) 9.80 (br. s, 1H, OH), 9.20 (d,  $J = 2.8$  Hz, 1H, ArH<sup>2</sup>), 9.19 (br. s, 1H, NH), 8.91 (br. s, 1H, NH), 8.03 (dd,  $J = 9.0, 2.8$  Hz, 1H, ArH<sup>3</sup>), 7.14 (d,  $J = 9.0$  Hz, 1H, ArH<sup>4</sup>), 7.00 (s, 2H, ArH<sup>1</sup>), 2.32 (s, 3H, *p*-CH<sub>3</sub>), 2.21 (s, 6H, *o*-CH<sub>3</sub>).

$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_3\text{CN}$ ) 158.3 (C), 158.0 (C), 151.9 (C), 141.0 (C), 137.7 (C), 135.3 (C), 130.4 (C), 128.7 (CH), 125.5 (C), 121.3 (CH), 115.2 (CH), 114.7 (CH), 20.0 (CH<sub>3</sub>), 17.3 (CH<sub>3</sub>).

HRMS (EI) Exact mass calculated for  $\text{C}_{17}\text{H}_{17}\text{O}_5\text{N}_3$   $[\text{M}]^+$ : 343.11627, found: 343.11534.

**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride**  
(237)<sup>456,457</sup>



Borane dimethyl sulfide complex (6.08 g, 80.0 mmol) was added dropwise to a solution of *N*-(2-hydroxyphenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (5.97 g, 20.0 mmol) in anhydrous tetrahydrofuran (80 mL) under a nitrogen atmosphere. Once the resulting effervescence had stopped, the reaction mixture was heated under reflux for 18 h. Methanol (40 mL) was added slowly to the reaction mixture, followed by concentrated aqueous hydrochloric acid (12 M, 6 mL); the volatiles were then removed *in vacuo*. Methanol (40 mL) was added, then the volatiles again removed *in vacuo*. This was repeated twice more. Triethyl orthoformate (60 mL) was added, and the resulting mixture heated to 100 °C for 0.5 h then allowed to cool to room temperature. The resulting precipitate was collected by vacuum filtration, and washed with diethyl ether ( $3 \times 20$  mL) to give 1-(2,4,6-trimethylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride (3.00 g, 9.50 mmol, 47%) as an amorphous white solid.

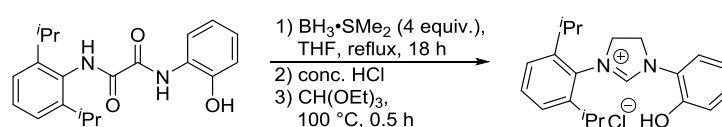
m.p.: decomposed when heated above 200 °C (diethyl ether).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 8.88 (s, 1H, NCHN), 7.60 (dd,  $J = 8.2, 1.2$  Hz, 1H, ArH), 7.05 (dd,  $J = 8.1, 1.5$  Hz, 1H, ArH), 7.02-6.97 (m, 3H, ArH), 6.79 (m, 1H, ArH), 4.84-4.76 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 4.43-4.35 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 2.37 (s, 3H,  $p\text{-CH}_3$ ), 2.34 (s, 6H,  $o\text{-CH}_3$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ) 157.3 (CH), 149.9 (C), 140.9 (C), 135.1 (C), 130.4 (C), 130.1 (CH), 128.8 (CH), 122.6 (C), 120.1 (CH), 119.7 (CH), 119.0 (CH), 50.7 ( $\text{CH}_2$ ), 50.1 ( $\text{CH}_2$ ), 21.1 ( $\text{CH}_3$ ), 17.9 ( $\text{CH}_3$ ).

Data were in accordance with that previously reported.<sup>456,457</sup>

### 1-(2,6-Diisopropylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride (238)



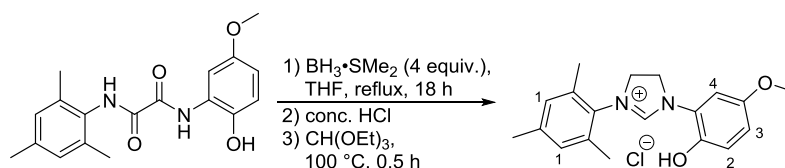
Borane dimethyl sulfide complex (3.04 g, 40.0 mmol) was added dropwise to a solution of *N*-(2-hydroxyphenyl)-*N'*-(2,6-diisopropylphenyl)-ethanediamide (3.40 g, 10.0 mmol) in anhydrous tetrahydrofuran (40 mL) under a nitrogen atmosphere. Once the resulting effervescence had stopped, the reaction mixture was heated under reflux for 18 h. Methanol (40 mL) was added slowly to the reaction mixture, followed by concentrated aqueous hydrochloric acid (5.4 mL); the solvent was then removed *in vacuo*. Methanol (25 mL) was added, then the solvent again removed *in vacuo*. This was repeated twice more. Triethyl orthoformate (30 mL) was added, and the resulting mixture heated to 100 °C for 0.5 h then allowed to cool to room temperature. The volatiles were removed *in vacuo*, and the resulting orange oil triturated with diethyl ether to give 1-(2,6-diisopropylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride as a cream amorphous solid (1.20 g, 3.35 mmol, 33 %).

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 12.16 (br. s, OH), 9.13 (s, 1H, NCHN), 7.73 (dd,  $J = 8.2, 1.3$  Hz, 1H, ArH), 7.52 (t,  $J = 7.9$  Hz, 1H, ArH), 7.32 (d,  $J = 7.9$  Hz, 2H, ArH), 7.20 (td,  $J = 7.8, 1.5$  Hz, 1H, ArH), 7.13 (dd,  $J = 8.0, 1.4$  Hz, 1H, ArH), 6.93 (td,  $J = 7.7, 1.3$  Hz, 1H, ArH), 4.77-4.68 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 4.35-4.27 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 2.99 (app. sep.,  $J = 6.8$  Hz, 2H,  $\text{CH}(\text{CH}_3)_2$ ), 1.32 (d,  $J = 6.8$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ), 1.27 (d,  $J = 6.8$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (125 MHz,  $\text{CD}_2\text{Cl}_2$ ) 159.4 (C), 152.4 (CH), 148.4 (C), 133.5 (CH), 131.6 (C), 131.1 (CH), 127.0 (CH), 124.7 (C), 122.0 (CH), 121.5 (CH), 120.9 (CH), 54.3 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ), 30.8 (CH), 26.6 ( $\text{CH}_3$ ), 25.8 ( $\text{CH}_3$ ).

Data were in accordance with that previously reported.<sup>456,457</sup>

**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-, 5-methoxyphenyl)-4,5-dihydro-imidazolium chloride (239)**



Borane dimethyl sulfide complex (5.47 g, 72.0 mmol) was added dropwise to a solution of *N*-(2-hydroxy-, 5-methoxyphenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (5.91 g, 18.0 mmol) in anhydrous tetrahydrofuran (75 mL) under a nitrogen atmosphere. Once the resulting effervescence had stopped, the reaction mixture was heated under reflux for 18 h. Methanol (40 mL) was added slowly to the reaction mixture, followed by concentrated aqueous hydrochloric acid (12 M, 5.4 mL); the volatiles were then removed *in vacuo*. Methanol (40 mL) was added, then the volatiles again removed *in vacuo*. This was repeated twice more. Triethyl orthoformate (54 mL) was added, and the resulting mixture heated to 100 °C for 0.5 h then allowed to cool to room temperature. The resulting dark green precipitate was collected by vacuum filtration, and washed with diethyl ether (3 × 20 mL) to give 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-, 5-methoxyphenyl)-4,5-dihydro-imidazolium chloride (3.76 g, 10.9 mmol, 60%) as an amorphous green solid.

m.p.: decomposed when heated above 180 °C (diethyl ether).

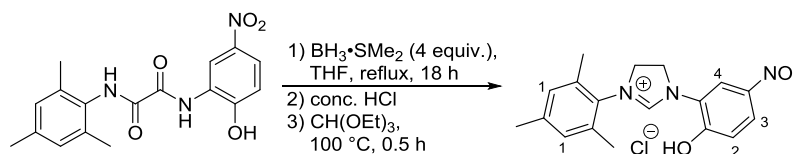
$\nu_{\text{max}}$ /cm<sup>-1</sup> (neat): 2830, 1600, 1508, 1414, 1263, 1204, 1043.

$\delta_{\text{H}}$  (600 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 11.39 (br. s, 1H, OH), 9.20 (s, 1H, NCHN), 7.58 (d, *J* = 9.0 Hz, 1H, ArH<sup>2</sup>), 7.05 (s, 2H, ArH<sup>1</sup>), 6.76 (dd, *J* = 9.0, 2.8 Hz, 1H, ArH<sup>3</sup>), 6.70 (d, *J* = 2.8 Hz, 1H, ArH<sup>4</sup>), 4.75-4.68 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 4.39-4.33 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 2.38-2.36 (m, 9H, ArCH<sub>3</sub>).

$\delta_{\text{C}}$  (150 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 158.4 (CH), 153.5 (C), 144.5 (C), 141.6 (C), 135.7 (C), 130.9 (C), 130.6 (CH), 124.0 (C), 120.3 (CH), 113.9 (CH), 107.3 (CH), 56.5 (CH<sub>3</sub>), 51.1 (CH<sub>2</sub>), 50.6 (CH<sub>2</sub>), 21.4 (CH<sub>3</sub>), 18.2 (CH<sub>3</sub>).

HRMS (ESI) Exact mass calculated for C<sub>19</sub>H<sub>23</sub>O<sub>2</sub>N<sub>2</sub> [M]<sup>+</sup>: 311.17540, found: 311.17580.

**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-, 5-nitrophenyl)-4,5-dihydro-imidazolium chloride (240)**



Borane dimethyl sulfide complex (2.28 g, 30.0 mmol) was added dropwise to a solution of *N*-(2-hydroxy-, 5-nitrophenyl)-*N'*-(2,4,6-trimethylphenyl)-ethanediamide (1.72 g, 5.00 mmol) in anhydrous tetrahydrofuran (30 mL) under a nitrogen atmosphere. Once the resulting effervescence had stopped, the reaction mixture was heated under reflux for 18 h. Methanol (20 mL) was added slowly to the reaction mixture, followed by concentrated aqueous hydrochloric acid (12 M, 1.5 mL); the volatiles were then removed *in vacuo*. Methanol (20 mL) was added, then the volatiles again removed *in vacuo*. This was repeated twice more. Triethyl orthoformate (15 mL) was added, and the resulting mixture heated to 100 °C for 0.5 h then allowed to cool to room temperature. The resulting pale yellow precipitate was collected by vacuum filtration, and washed with diethyl ether (3 × 20 mL) to give 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-, 5-nitrophenyl)-4,5-dihydro-imidazolium chloride (0.886 g, 2.45 mmol, 49%) as an amorphous brown solid.

m.p.: decomposed when heated above 180 °C (diethyl ether).

$\nu_{\max}/\text{cm}^{-1}$  (neat): 2459 (br.) 1632, 1589, 1533, 1499, 1337, 1287, 1258, 1202, 1103.

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_3\text{CN}$ ) 13.53 (br. s, 1H, OH), 8.88 (s, 1H, NCHN), 8.19 (d,  $J = 2.7$  Hz, 1H, ArH<sup>4</sup>), 8.16 (dd,  $J = 9.1, 2.7$  Hz, 1H, ArH<sup>3</sup>), 7.96 (d,  $J = 9.1$  Hz, 1H, ArH<sup>2</sup>), 7.09 (s, 2H, ArH<sup>1</sup>), 4.72-4.67 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 4.36-4.30 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>), 2.36 (s, 6H, *o*-CH<sub>3</sub>), 2.35 (s, 3H, *p*-CH<sub>3</sub>).

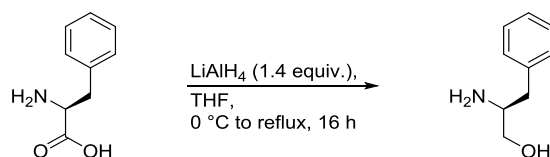
$\delta_{\text{C}}$  (125 MHz,  $\text{CD}_3\text{CN}$ ) 159.7 (CH), 158.8 (C), 141.7 (C), 140.7 (C), 136.6 (C), 131.9 (C), 130.7 (CH), 125.6 (CH), 124.9 (C), 119.5 (CH), 50.9 (CH<sub>2</sub>), 50.4 (CH<sub>2</sub>), 20.1 (CH<sub>3</sub>), 16.8 (CH<sub>3</sub>).

HRMS (ESI) Exact mass calculated for  $\text{C}_{18}\text{H}_{20}\text{O}_3\text{N}_3$  [M]<sup>+</sup>: 326.14992, found: 326.14870.



## 5.9 IMIDAZOLIUM SALT SYNTHESIS

### (S)-(+)-2-Amino-3-phenyl-1-propanol<sup>482</sup>



(S)-2-Amino-3-phenylpropanoic acid (6.61 g, 40.0 mmol) was added at 0 °C to a solution of lithium aluminium hydride (2.13 g, 56.0 mmol) in tetrahydrofuran (80 mL) and the resulting mixture was stirred at 0 °C for 1 hour. The reaction mixture was then allowed to warm to room temperature and stirred for 1 hour, then heated under reflux for 16 hours. The reaction mixture was then cooled to 0 °C and slowly diluted with diethyl ether (120 mL), water (30 mL) and aqueous sodium hydroxide (1.0 M, 10 mL). The resulting emulsion was filtered through celite, and washed with diethyl ether ( $3 \times 20$  mL), and the solvent removed *in vacuo*. Following recrystallisation from toluene, (S)-(+)-2-amino-3-phenyl-1-propanol was isolated as pale yellow plates (2.21 g, 14.6 mmol, 37%).

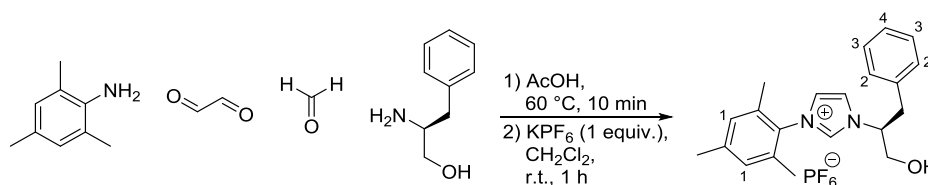
m.p.: 83-86 °C (toluene).

$\delta_{\text{H}}$  (600 MHz,  $\text{CDCl}_3$ ) 7.36-7.31 (m, 2H, ArH), 7.27-7.23 (m, 1H, ArH), 7.23-7.20 (m 2H, ArH), 3.66 (dd,  $J = 10.6, 4.0$  Hz, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{OH}$ ), 3.41 (dd,  $J = 10.6, 7.2$  Hz, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{OH}$ ), 3.18-3.12 (m, 1H, NCH), 2.82 (dd,  $J = 13.5, 5.3$  Hz, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{Ar}$ ), 2.56 (dd,  $J = 13.5, 8.5$  Hz, 1H,  $\text{CH}^{\text{a}}\text{H}^{\text{b}}\text{Ar}$ ), 1.77 (br. s, 3H, OH and NH).

$\delta_{\text{C}}$  (150 MHz,  $\text{CDCl}_3$ ) 138.7 (C), 129.2 (CH), 128.6 (CH), 126.4 (CH), 66.4 ( $\text{CH}_2$ ), 54.2 (CH), 41.0 ( $\text{CH}_2$ ).

Data were in accordance with that previously reported.<sup>482</sup>

**1-(2,4,6-Trimethylphenyl)-3-[(*S*)-2*N*-3-phenylpropanol]-imidazolium hexafluorophosphate (242)**



Synthesised according to the one-pot protocol reported by the group of Mauduit.<sup>459</sup>

The reaction was performed in open vessels under air atmosphere. A mixture of 2,4,6-trimethylaniline (1.35 g, 10.0 mmol), (*S*)-(+)-2-amino-3-phenyl-1-propanol (1.03 g, 10.0 mmol) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) was heated at 60 °C for 5 min (mixture A). A mixture of glyoxal (1.15 mL, 10.0 mmol, 40%wt in aqueous solution), formaldehyde (0.750 mL, 10.0 mmol, 37%wt in aqueous solution) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) also was heated at 60 °C for 5 min (mixture B). Mixture B was added in a single portion to A, and the resulting mixture was stirred at 60 °C for 10 min then cooled to room temperature. *tert*-Butyl methyl ether (50 mL) and water (50 mL) were added and the aqueous phase was washed with *tert*-butyl methyl ether (3 × 50 mL). Brine (50 mL) was added and the aqueous phase was washed with *tert*-butyl methyl ether (3 × 50 mL). Dichloromethane (25 mL) and potassium hexafluorophosphate (1.68 g, 10.0 mmol) were added to the aqueous phase, and the resulting biphasic mixture was stirred at room temperature for 1 hour. The organic phase was separated, dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. Following flash column chromatography (conditions: column - Biotage® SNAP KP-Sil, 100 g; solvent system – dichloromethane/methanol, gradient from 99:1 to 95:5 over 10 column volumes) *1-(2,4,6-trimethylphenyl)-3-[(S)-2*N*-3-phenylpropanol]-imidazolium hexafluorophosphate* was isolated as a brown amorphous solid (1.44 g, 3.23 mmol, 32%).

$R_f$  = 0.25 (dichloromethane: methanol, 98:2).

m.p.: 137 to 139 °C (methanol).

$\delta_H$  (600 MHz,  $CD_2Cl_2$ ) 8.19 (app. t,  $J$  = 1.5 Hz, 1H, NCHN), 7.66 (app. t,  $J$  = 1.70 Hz, 1H, NCHCHN), 7.32-7.28 (m, 2H, ArH<sup>2</sup>), 7.27-7.23 (m, 1H, ArH<sup>4</sup>), 7.19-7.15 (m, 3H, NCHCHN and ArH<sup>3</sup>), 7.03 (s, 1H, ArH<sup>1</sup>), 7.00 (s, 1H, ArH<sup>1</sup>), 4.94-4.88 (m, 1H, NCH(CH<sub>2</sub>)CH<sub>2</sub>), 4.23 (m, 1H, CH<sup>a</sup>H<sup>b</sup>OH), 4.08 (m, 1H, CH<sup>a</sup>H<sup>b</sup>OH), 3.37 (dd,  $J$  = 14.5, 5.0 Hz, 1H, ArCH<sup>a</sup>CH<sup>b</sup>), 3.18 (dd,  $J$  = 14.5, 10.8 Hz, 1H, ArCH<sup>a</sup>CH<sup>b</sup>), 2.56 (dd,  $J$  = 5.9, 4.5 Hz, 1H, OH), 2.34 (s, 3H, *p*-CH<sub>3</sub>), 1.97 (s, 3H, *o*-CH<sub>3</sub>), 1.70 (s, 3H, *o*-CH<sub>3</sub>).

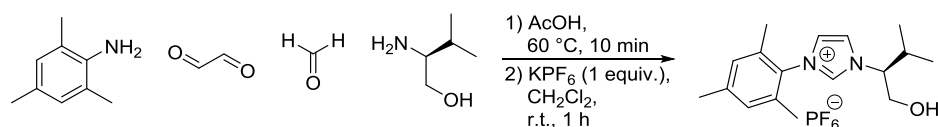
$\delta_C$  (100 MHz,  $(CD_3)_2SO$ ) 140.2 (C), 137.0 (CH), 136.3 (C), 134.2 (C), 134.1 (C), 131.0 (C), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 126.8 (CH), 124.0 (CH), 121.8 (CH), 64.5 (CH), 62.3 (CH<sub>2</sub>), 35.8 (CH<sub>2</sub>), 20.5 (CH<sub>3</sub>), 16.7 (CH<sub>3</sub>), 16.4 (CH<sub>3</sub>).

$\delta_F$  (377 MHz,  $(CD_3)_2SO$ ) -70.20 (d,  $J = 711.2$  Hz).

$\delta_P$  (203 MHz,  $(CD_3)_2SO$ ) 144.18 (sep.,  $J = 711.1$  Hz)

HRMS (ESI) Exact mass calculated for  $C_{21}H_{25}O_1N_2$   $[M]^+$ : 321.19614, found: 321.19740.

**1-(2,4,6-Trimethylphenyl)-3-((*S*)-2*N*-3-methylbutanol)-imidazolium hexafluorophosphate (244)**



The reaction was performed in open vessels under air atmosphere. A mixture of 2,4,6-trimethylaniline (1.35 g, 10.0 mmol), (*S*)-(+)-2-amino-3-methyl-1-butanol (1.03 g, 10.0 mmol) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) was heated at 60 °C for 5 min (mixture A). A mixture of glyoxal (1.15 mL, 10.0 mmol, 40%wt in aqueous solution), formaldehyde (0.750 mL, 10.0 mmol, 37% wt in aqueous solution) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) also was heated at 60 °C for 5 min (mixture B). The two mixtures were mixed, and the resulting mixture was stirred at 60 °C for 10 min then cooled to room temperature. Diethylether (50 mL) and water (50 mL) were added and the aqueous layer was washed with diethylether (3 × 50 mL). Brine (50 mL) was added and the aqueous layer was washed with diethylether (3 × 50 mL). Dichloromethane (25 mL) and potassium hexafluorophosphate (1.68 g, 10.0 mmol) were added to the aqueous layer, and the resulting biphasic mixture was stirred at room temperature for 1 hour. The organic layer was separated, dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. Following flash column chromatography (conditions: silica, 100 g; 55 mm Ø; dichloromethane/acetone, 9:1 v/v over 10 column volumes) 1-(2,4,6-trimethylphenyl)-3-((*S*)-2*N*-3-methylbutanol)-imidazolium hexafluorophosphate was isolated as a dark brown oil (1.11 g, 2.60 mmol, 26%).

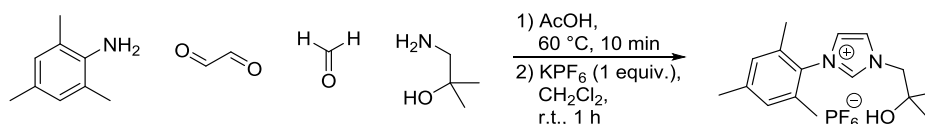
$\delta_H$  (600 MHz,  $CDCl_3$ ) 8.56 (m, 1H, NCHN), 7.70 (m, 1H, NCHCHN), 7.25 (m, 1H, NCHCHN), 7.05 (s, 2H, ArH), 4.37 (ddd,  $J = 9.8, 7.2, 3.2$  Hz, 1H, NCH(CH)CH<sub>2</sub>), 4.14 (dd,  $J = 12.3, 3.2$  Hz, 1H, CH<sup>a</sup>H<sup>b</sup>OH), 3.99 (dd,  $J = 12.3, 7.2$  Hz, 1H, CH<sup>a</sup>H<sup>b</sup>OH), 2.38 (s, 3H, *p*-ArCH<sub>3</sub>), 2.34-2.28 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.06 (s, 3H, *o*-ArCH<sub>3</sub>), 2.05 (s, 3H, *o*-ArCH<sub>3</sub>), 1.14 (d,  $J = 6.6$  Hz, 3H, CHCH<sub>3</sub>), 0.90 (d,  $J = 6.7$  Hz, 3H, CHCH<sub>3</sub>).

$\delta_c$  (150 MHz,  $CDCl_3$ ) 141.6 (C), 136.4 (CH), 134.5 (C), 134.0 (C), 130.4 (C), 130.0 (C), 129.8 (CH), 123.7 (CH), 121.9 (CH), 69.3 (CH), 61.7 ( $CH_2$ ), 30.9 ( $CH_3$ ), 29.4 ( $CH_3$ ), 21.1 (CH), 19.2 ( $CH_3$ ), 19.1 ( $CH_3$ ), 17.02 ( $CH_3$ ).

$\delta_F$  (470 MHz,  $CDCl_3$ ) -72.22 (d,  $J = 712.9$  Hz).

Data in accordance with that previously reported.<sup>459</sup>

**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-2-methylpropyl)-imidazolium hexafluorophosphate (245)**



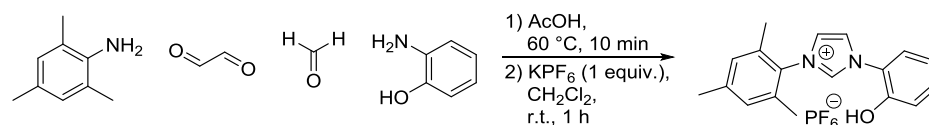
The reaction was performed in open vessels under air atmosphere. A mixture of 2,4,6-trimethylaniline (1.35 g, 10.0 mmol), 1-amino-2-methyl-2-propanol (1.52 g, 10.0 mmol) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) was heated at 60 °C for 5 min (mixture A). A mixture of glyoxal (1.15 mL, 10.0 mmol, 40% wt in aqueous solution), formaldehyde (0.75 mL, 10.0 mmol, 37% wt in aqueous solution) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) also was heated at 60 °C for 5 min (mixture B). Mixture B was added in a single portion to A, and the resulting mixture was stirred at 60 °C for 10 min then cooled to room temperature. *tert*-Butyl methyl ether (50 mL) and water (50 mL) were added and the aqueous layer was washed with *tert*-butyl methyl ether (3 × 50 mL). Brine (50 mL) was added and the aqueous layer was washed with *tert*-butyl methyl ether (3 × 50 mL). Dichloromethane (25 mL) and potassium hexafluorophosphate (1.68 g, 10.0 mmol) were added to the aqueous layer, and the resulting biphasic mixture was stirred at room temperature for 1 hour. The organic layer was separated, dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. Following flash column chromatography (conditions: column - Biotage® SNAP KP-Sil, 100 g; solvent system – dichloromethane/ethyl acetate, gradient from 99:1 to 90:10 over 20 column volumes) 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-2-methylpropyl)-imidazolium hexafluorophosphate was isolated as a beige amorphous solid (1.69 g, 4.17 mmol, 42%).

$\delta_{\text{H}}$ (400 MHz,  $(\text{CD}_3)_2\text{SO}$ ) 9.34-9.29 (m, 1H, NCHN), 7.95-7.91 (m, 2H, ), 7.16 (s, 2H), 5.15 (s, 1H, OH), 4.19 (s, 2H, NCH<sub>2</sub>), 2.33 (s, 3H, *p*-CH<sub>3</sub>), 2.02 (s, 6H, *o*-CH<sub>3</sub>), 1.14 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_{\text{C}}$ (100 MHz,  $(\text{CD}_3)_2\text{SO}$ ) 140.2 (C), 137.9 (C), 134.2 (CH), 131.2 (C), 129.2 (CH), 124.7 (CH), 123.1 (CH), 68.0 (CH<sub>2</sub>), 59.3 (C), 26.7 (CH<sub>3</sub>), 20.6 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>).

$\delta_{\text{F}}$ (377 MHz,  $(\text{CD}_3)_2\text{SO}$ ) -70.15 (d,  $J = 709.5$  Hz)

### 1-(2,4,6-Trimethylphenyl)-3-(2-hydroxyphenyl)-imidazolium hexafluorophosphate (246)



The reaction was performed in open vessels under air atmosphere. A mixture of 2,4,6-trimethylaniline (1.35 g, 10.0 mmol), 2-aminophenol (1.09 g, 10.0 mmol) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) was heated at 60 °C for 5 min (mixture A). A mixture of glyoxal (1.15 mL, 10.0 mmol, 40% wt in aqueous solution), formaldehyde (0.75 mL, 10.0 mmol, 37% wt in aqueous solution) and acetic acid (2.70 g, 2.58 mL, 45.0 mmol) also was heated at 60 °C for 5 min (mixture B). Mixture B was added in a single portion to A, and the resulting mixture was stirred at 60 °C for 10 min then cooled to room temperature. *tert*-Butyl methyl ether (50 mL) and water (50 mL) were added and the aqueous layer was washed with *tert*-butyl methyl ether (3 × 50 mL). Brine (50 mL) was added and the aqueous layer was washed with *tert*-butyl methyl ether (3 × 50 mL). Dichloromethane (25 mL) and potassium hexafluorophosphate (1.68 g, 10.0 mmol) were added to the aqueous layer, and the resulting biphasic mixture was stirred at room temperature for 1 hour. The organic layer was separated, dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. Following flash column chromatography (conditions: column - Biotage® SNAP KP-Sil, 50 g; solvent system – dichloromethane/ethyl acetate, gradient from 99:1 to 95:5 over 10 column volumes) 1-(2,4,6-trimethylphenyl)-3-(2-hydroxyphenyl)-imidazolium hexafluorophosphate was isolated as a beige amorphous solid (0.348 g, 0.82 mmol, 8%).

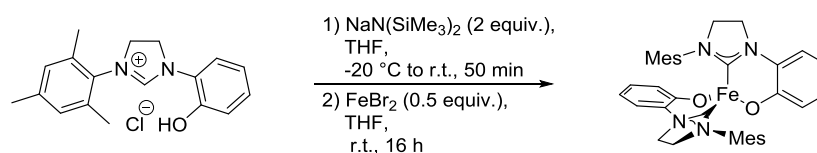
$\delta_{\text{H}}$  (400 MHz,  $(\text{CD}_3)_2\text{SO}$ ) 9.80 (app. t,  $J = 1.5$  Hz, 1H, NCHN), 8.34 (app. t,  $J = 1.8$  Hz, 1H, NCHCHN), 8.14 (app. t,  $J = 1.8$  Hz, 1H, NCHCHN), 7.68 (dd,  $J = 7.9, 1.5$  Hz, 1H, ArH), 7.48-7.42 (m, 1H, ArH), 7.19 (s, 2H, ArH), 7.16 (dd,  $J = 8.2, 1.0$  Hz, 1H, ArH), 7.07 (ddd,  $J = 7.9, 7.4, 1.1$  Hz, 1H, ArH), 2.35 (s, 3H, *p*-CH<sub>3</sub>), 2.11 (s, 6H, *o*-CH<sub>3</sub>).

$\delta_C$  (100 MHz,  $(CD_3)_2SO$ ) 150.9 (C), 140.4 (C), 138.2 (C), 134.3 (CH), 131.6 (C), 131.1 (C), 129.3 (CH), 126.2 (CH), 124.3 (CH), 123.7 (CH), 122.2 (CH), 119.6 (CH), 117.0 (CH), 20.6 ( $CH_3$ ), 16.9 ( $CH_3$ ).

$\delta_F$  (377 MHz,  $(CD_3)_2SO$ ) -70.13 (d,  $J = 711.8$  Hz).

## 5.10 IRON *N*-HETEROCYCLIC CARBENE COMPLEX SYNTHESES

### Bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) (250)



Sodium bis(trimethylsilyl)amide solution (2.0 M in tetrahydrofuran, 5.00 mL, 10.0 mmol) was added dropwise to a stirred solution of 1-(2,4,6-trimethylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride (1.58 g, 5.00 mmol) in tetrahydrofuran (50 mL) under a nitrogen atmosphere at -20 °C. The resulting solution was stirred for 20 mins then allowed to warm to room temperature over 30 mins. The resulting bright green solution was added dropwise to a stirred solution of iron(II) bromide (0.539 g, 2.50 mmol) in tetrahydrofuran (25 mL) at room temperature in an inert atmosphere glovebox. After 18 h, the resulting suspension was filtered in the glovebox and the filter plug washed with tetrahydrofuran (75 mL). Solvent and volatiles were removed from the resulting solution dark green solution *in vacuo* to leave *bis*[1-(*mesityl*)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) as a dark green solid (0.609 g, 0.99 mmol, 40%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of tetrahydrofuran. Effective magnetic moment ( $\mu_{\text{eff}}$ ) was measured by Evans method NMR spectroscopy<sup>460–462</sup> against a tetrakis(trimethylsilyl)silane internal standard.

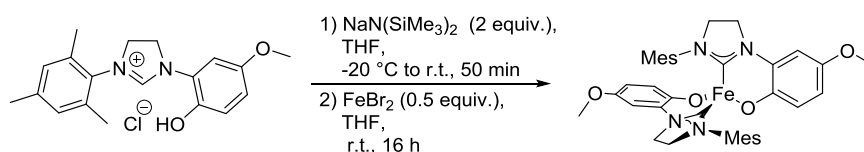
m.p.: decomposed when heated above 230 °C (tetrahydrofuran).

$\delta_H$  (500 MHz,  $d_8$ -THF) 46.86 (br. s), 35.91 (br. s), 20.22 (br. s), 5.98 (br. s), 4.55 (br. s), 3.27 (br. s), -3.91 (br. s), -5.40 (br. s), -30.65 (br. s), -32.68 (br. s), -33.40 (br. s).

$\mu_{\text{eff}} = 5.82$ .

HRMS (EI) Exact mass calculated for  $C_{36}H_{38}O_2N_4Fe$   $[M]^+$ : 614.23387, found: 614.23169.

**Bis[1-(2,4,6-trimethylphenyl)-3-(5-methoxy-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II)**  
(251)

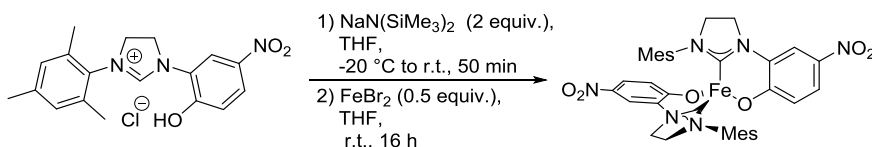


Sodium bis(trimethylsilyl)amide solution (2.0 M in tetrahydrofuran, 5.00 mL, 10.0 mmol) was added dropwise to a stirred solution of 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-, 5-methoxyphenyl)-4,5-dihydro-imidazolium chloride (1.73 g, 5.00 mmol) in tetrahydrofuran (20 mL) under a nitrogen atmosphere at -20 °C. The resulting solution was stirred for 20 mins then allowed to warm to room temperature over 30 mins. The resulting yellow solution was added dropwise to a stirred solution of iron(II) bromide (0.539 g, 2.50 mmol) in tetrahydrofuran (20 mL) at room temperature in an inert atmosphere glovebox. After 18 h, the resulting suspension was filtered in the glovebox and the filter plug washed with tetrahydrofuran (75 mL). Solvent and volatiles were removed from the resulting solution dark solution *in vacuo* to leave *bis*[1-(*mesityl*)-3-(4-methoxy-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) as a brown solid (0.808 g, 1.20 mmol, 48%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of tetrahydrofuran.

m.p.: decomposed when heated above 200 °C (tetrahydrofuran).

$\delta_{\text{H}}$  (500 MHz,  $\text{C}_6\text{D}_6$ ) 42.11 (br. s), 38.98 (br. s), 16.45 (br. s), 9.17 (br. s), 6.06 (br. s), 4.79 (br. s), 3.42 (br. s), -1.23 (br. s), -3.96 (br. s), -4.95 (br. s), -34.92 (br. s).

**Bis[1-(2,4,6-trimethylphenyl)-3-(5-nitro-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II)**  
(252)



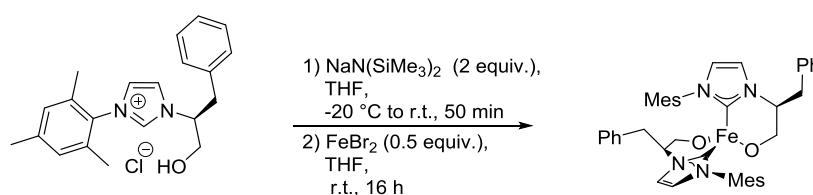
Sodium bis(trimethylsilyl)amide solution (2.0 M in tetrahydrofuran, 2.00 mL, 4.00 mmol) was added dropwise to a stirred solution of 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-, 5-nitrophenyl)-4,5-dihydro-imidazolium chloride (0.724 g, 2.00 mmol) in tetrahydrofuran (20 mL) under a nitrogen atmosphere at -20 °C. The resulting solution was stirred for 20 mins then allowed to warm to room temperature over 30 mins. The resulting yellow solution was added dropwise to a stirred solution of iron(II) bromide (0.216 g, 1.00 mmol) in tetrahydrofuran (10 mL) at room

temperature in an inert atmosphere glovebox. After 18 h, the resulting suspension was filtered in the glovebox and the filter plug washed with tetrahydrofuran (75 mL). Solvent and volatiles were removed from the resulting solution dark solution *in vacuo* to leave bis[1-(mesityl)-3-(4-nitro-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) as a dark brown solid (0.605 g, 0.86 mmol, 43%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of tetrahydrofuran.

m.p.: decomposed when heated above 200 °C (tetrahydrofuran).

$\delta_{\text{H}}$  (500 MHz,  $\text{C}_6\text{D}_6$ ) 49.75 (br. s), 29.48 (br. s), 22.25 (br. s), 5.44 (br. s), 4.16 (br. s), 3.72 (br. s), -4.69 (br. s), -7.10 (br. s), -24.50 (br. s), -29.04 (br. s).

### Bis{1-[2,4,6-trimethylphenyl]-3-[(*S*)-2*N*-3-phenylpropanoxy]imidazolyl} iron(II) (253)



Sodium bis(trimethylsilyl)amide solution (2.0 M in tetrahydrofuran, 2.00 mL, 4.00 mmol) was added dropwise to a stirred solution of 1-(2,4,6-trimethylphenyl)-3-(2-hydroxy-, 5-nitrophenyl)-4,5-dihydro-imidazolium chloride (0.724 g, 2.00 mmol) in tetrahydrofuran (20 mL) under a nitrogen atmosphere at -20 °C. The resulting solution was stirred for 20 mins then allowed to warm to room temperature over 30 mins. The resulting yellow solution was added dropwise to a stirred solution of iron(II) bromide (0.216 g, 1.00 mmol) in tetrahydrofuran (10 mL) at room temperature in an inert atmosphere glovebox. After 18 h, the resulting suspension was filtered in the glovebox and the filter plug washed with tetrahydrofuran (75 mL). Solvent and volatiles were removed from the resulting solution dark solution *in vacuo* to leave bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) as a pale yellow amorphous solid, as a mixture with sodium hexafluorophosphate (0.590 g, 0.85 mmol, 85%). The complex was used catalytically without further purification. Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of benzene and dichloromethane, and were determined to be  $\text{Fe}_4\text{L}_6 \cdot 2\text{PF}_6$  as an adduct with adventitious  $\text{PF}_6^-$  counter-ions.

m.p.: decomposed when heated above 90 °C (tetrahydrofuran).

$\delta_{\text{H}}$  (500 MHz,  $d_8$ -THF) 43.53 (br. s), 37.13 (br. s), 25.49 (br. s), 24.67 (br. s), 13.84 (br. s), 9.47 (s), 8.74 (s), 5.82 (br. s), 2.75 (br. s), 2.05 (s), 1.27 (br. s), 0.90 (br. s), -23.64 (br. s).

HRMS (EI) Exact mass calculated for  $\text{C}_{42}\text{H}_{46}\text{O}_2\text{N}_4\text{Fe} [\text{M}]^+$ : 694.29647, found: 694.29721.



## 5.11 HYDROBORATION REACTIONS WITH CATECHOLBORANE: REACTION MONITORING BY NMR SPECTROSCOPY

All reactions were carried out at room temperature ( $25 \pm 3$  °C) in a Radley's carousel multiple position reactor under a purified nitrogen atmosphere.

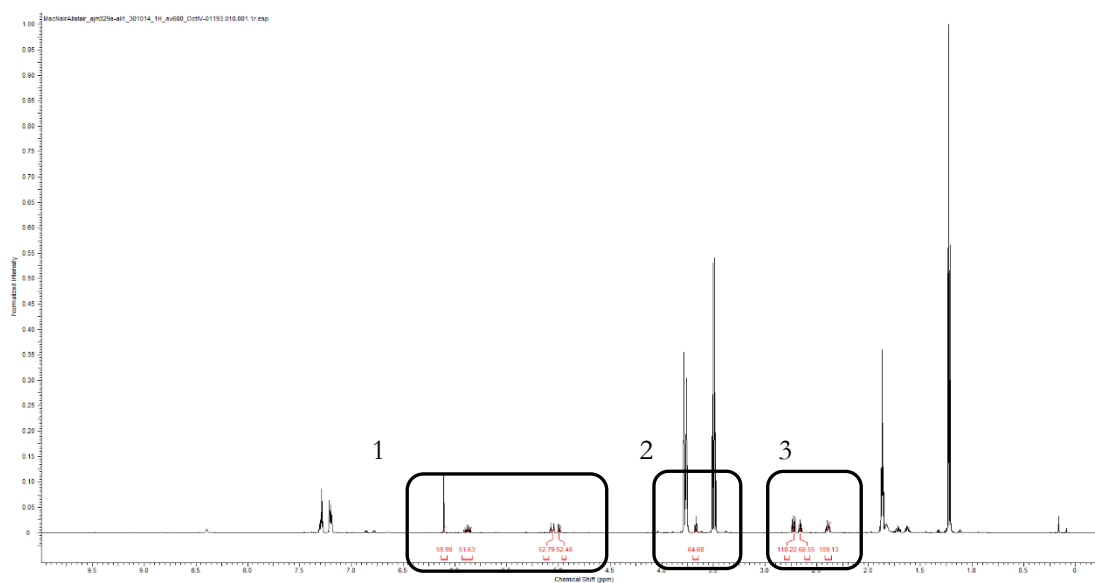
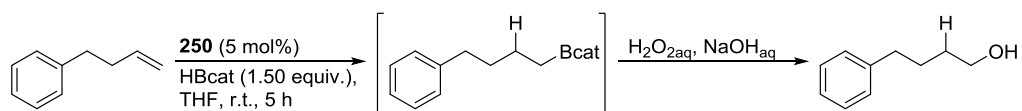
Catechol borane was purchased from Acros Organics, Alfa Aesar or Sigma Aldrich and distilled under reduced pressure immediately before use (20 mbar, 40 °C).

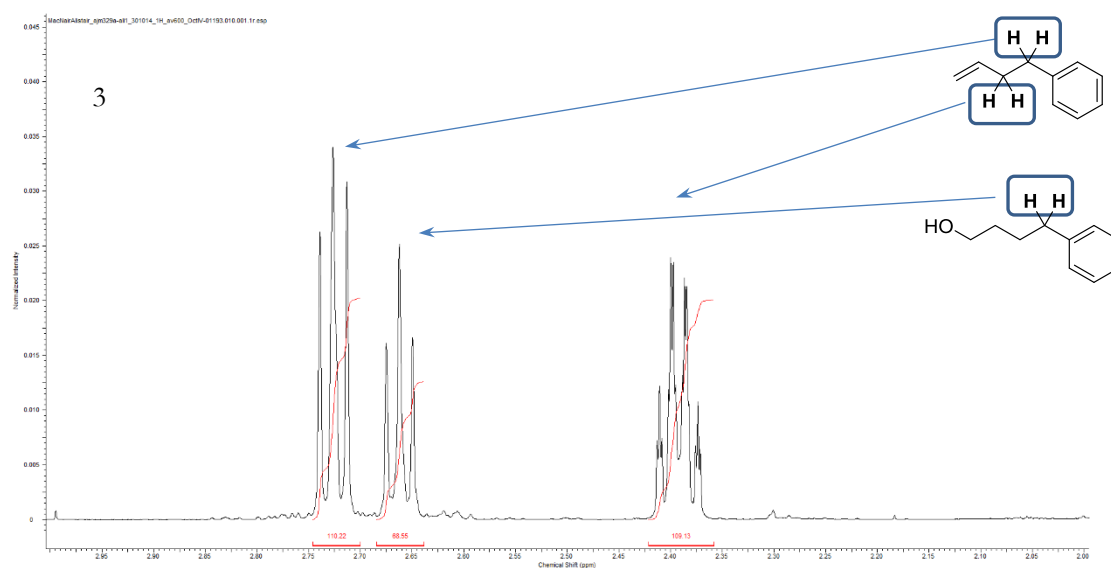
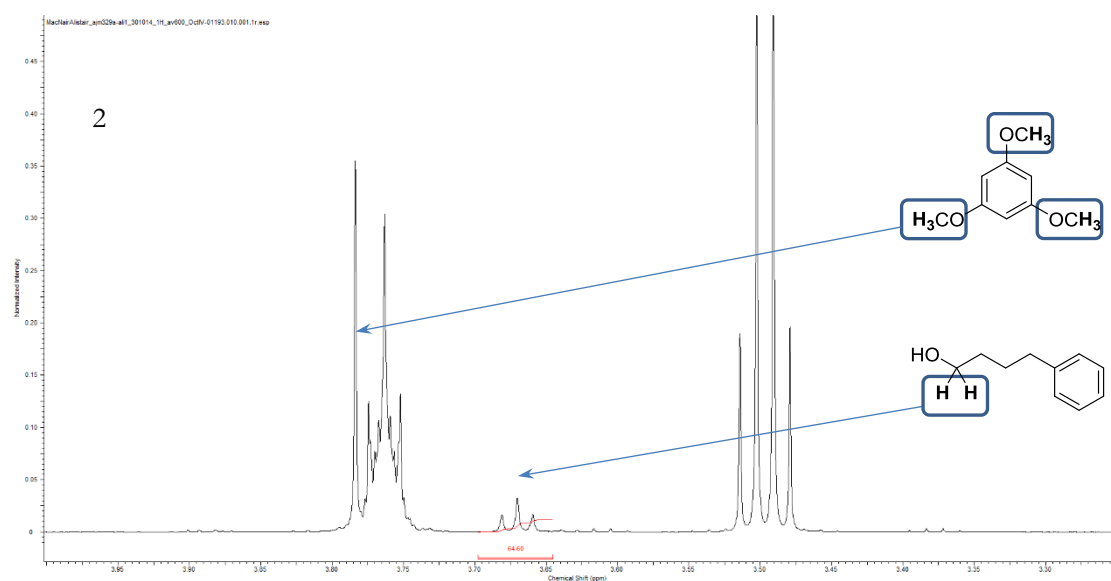
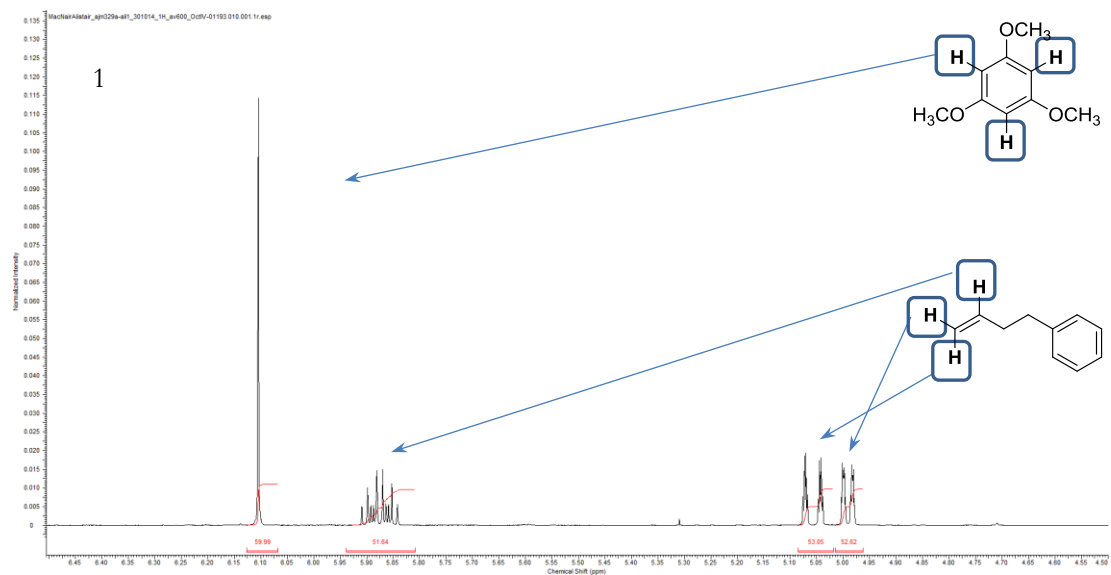
### General Procedure G: Hydroboration of alkenes with catecholborane

Reaction condition optimisation experiments, and initial substrate scope investigations, were monitored by  $^1\text{H}$  NMR spectroscopy according to the following protocol.

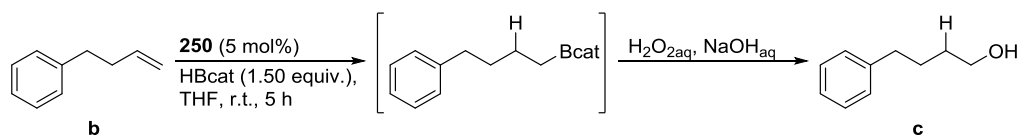
Catecholborane (0.180 g, 0.160 mL, 1.50 mmol, 1.50 equivalents) was added in one portion to a mixture of an 4-phenyl-1-butene (0.132 g, 0.150 mL, 1.00 mmol, 1.00 equivalents) and bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol, 0.05 equivalents) in anhydrous tetrahydrofuran (1 mL). Anhydrous tetrahydrofuran (1 mL) was then added, ensuring that the sides of the reaction vessel were washed. At pre-determined time points, aliquots ( $\leq 5$   $\mu\text{L}$ ) were removed from the reaction mixture, and added to an aqueous solution of NaOH (1 M, 1.5 mL)/H<sub>2</sub>O<sub>2</sub> (30%wt in water, 1 mL) at 0 °C and the resulting mixture stirred for 0.5 h. The organic phase was then extracted with diethyl ether (1 mL), dried over magnesium sulfate, and the volatiles allowed to evaporate for 1 h. The resulting mixture was diluted with *d*-chloroform and assessed by  $^1\text{H}$  NMR spectroscopy by comparison to authentic samples.

## Example Analysis



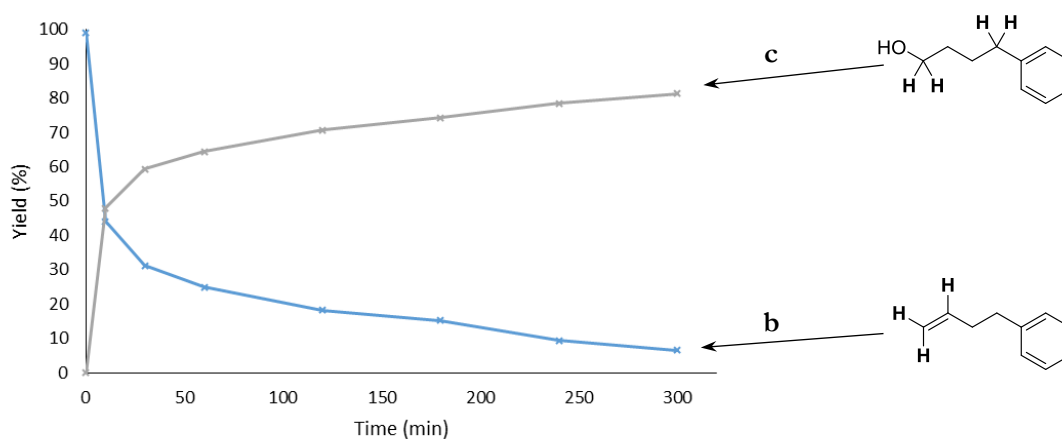
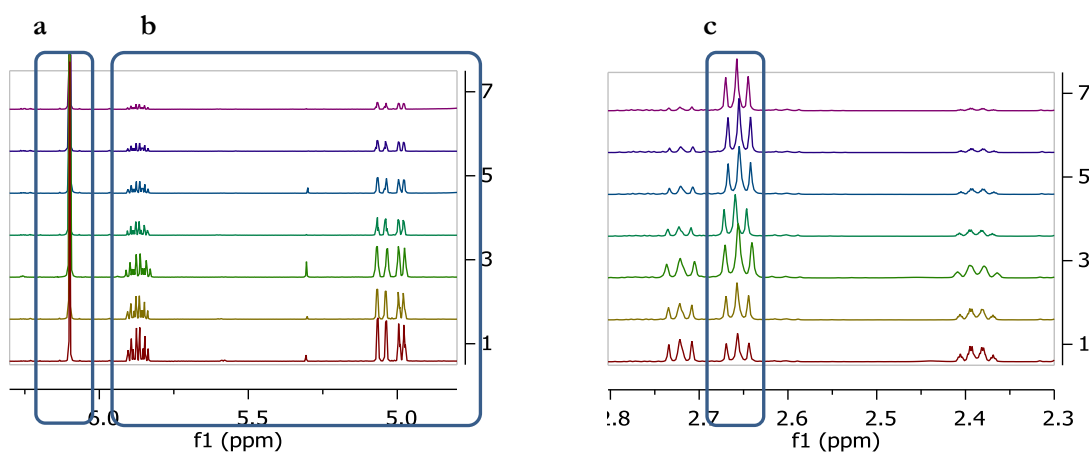


## Example Run



Spectra number	Time (min)	Yield (%) <sup>a</sup>	
		4-phenyl-1-butene ( <b>b</b> )	Linear alcohol ( <b>c</b> )
-	0	99	0
1	10	44	48
2	30	31	59
3	60	25	64
4	120	18	71
5	180	17	72
6	240	15	74
7	300	9	79

Reaction performed according to general procedure D. <sup>a</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy relative to 1,3,5-trimethoxybenzene (**a**) internal standard (0.20 equivalents).



## 5.12 HYDROBORATION REACTIONS WITH CATECHOLBORANE: ISOLATED PRODUCTS

All reactions were carried out at room temperature ( $25 \pm 3$  °C) in a Radley's carousel multiple position reactor under a purified nitrogen atmosphere.

Catechol borane was purchased from Acros Organics, Alfa Aesar or Sigma Aldrich and distilled under reduced pressure immediately before use (20 mbar, 40 °C).

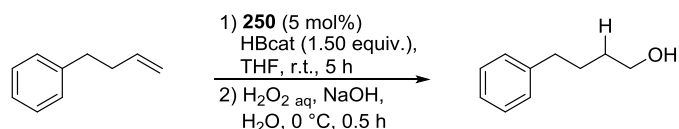
### General Procedure H: Hydroboration of alkenes with catecholborane then oxidation

Catecholborane (0.180 g, 0.160 mL, 1.50 mmol, 1.50 equivalents) was added in one portion to a mixture of an alkene (1.00 mmol, 1.00 equivalent) and bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol, 0.05 equivalents) in anhydrous tetrahydrofuran (1 mL). Anhydrous tetrahydrofuran (1 mL) was then added, ensuring that the sides of the reaction vessel were washed. After 5 h the reaction mixture was cooled to 0 °C and an aqueous solution of sodium hydroxide (1 M, 3 mL) and hydrogen peroxide (30%wt in water, 2 mL) was added and the resulting mixture stirred for 0.5 h, the organic phase was then extracted with diethyl ether ( $3 \times 10$  mL), washed with a saturated solution of sodium thiosulfate (10 mL), washed with a saturated solution of sodium chloride (10 mL), dried over magnesium sulfate, and concentrated *in vacuo*.<sup>411</sup> 1,3,5-Trimethoxybenzene (0.034 g, 0.20 mmol, 0.20 equivalents) was added as an internal standard, and the crude product mixture was analysed by <sup>1</sup>H NMR spectroscopy and/or GCMS.

### General Procedure I: Hydroboration of alkenes with catecholborane then transesterification

Catecholborane (0.180 g, 0.160 mL, 1.50 mmol, 1.50 equivalents) was added in one portion to a mixture of an alkene (1.00 mmol, 1.00 equivalent) and bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol, 0.05 equivalents) in anhydrous tetrahydrofuran (1 mL). Anhydrous tetrahydrofuran (1 mL) was then added, ensuring that the sides of the reaction vessel were washed. After 5 h, pinacol (0.236 g, 2.00 mmol, 2.00 equivalents) was added and the resulting mixture was stirred for 18 h. Volatiles were removed from the reaction mixture *in vacuo*, then products were isolated following flash column chromatography (conditions: silica, 10-15 g; 30 mm Ø; solvent system – pentane/diethyl ether).

#### 4-Phenylbutan-1-ol (260)<sup>483</sup>



According to general procedure **H**, 4-phenyl-1-butene (0.132 g, 0.150 mL, 1.00 mmol), was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL). Following oxidation and flash column chromatography (conditions: silica, 15 g; 30 mm Ø; gradient pentane/diethyl ether, from 80:20 to 40:60 v/v over 10 column volumes) 4-phenylbutan-1-ol was isolated as a pale yellow oil (0.103 g, 0.69 mmol, 69%).

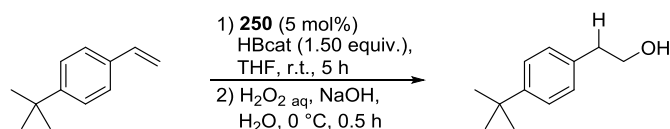
R<sub>f</sub> = 0.13 (pentane/diethyl ether, 60:40 v/v).

δ<sub>H</sub> (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.29-7.25 (m, 2H, ArH), 7.21-7.14 (m, 3H, ArH), 3.64-3.59 (m, 2H, CH<sub>2</sub>OH), 2.64 (t, *J* = 7.6 Hz, 2H, ArCH<sub>2</sub>), 1.72-1.64 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.61-1.54 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>OH), 1.29 (br. s, 1H, OH).

δ<sub>C</sub> (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 143.2 (C), 129.0 (CH), 128.8 (CH), 126.2 (CH), 63.2 (CH<sub>2</sub>), 36.2 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>).

Data were in accordance with that previously reported.<sup>483</sup>

#### 2-(4-*tert*-Butylphenyl)ethan-1-ol (262)<sup>484</sup>



According to general procedure **H**, 4-*tert*-butylstyrene (0.160 g, 0.183 mL, 1.00 mmol) was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL). Following oxidation and flash column chromatography (conditions: silica, 14 g; 30 mm Ø; gradient pentane/diethyl ether, from 80:20 to 60:40 v/v over 10 column volumes) 2-(4-*tert*-butylphenyl)ethanol was isolated as a yellow oil (0.126 g, 0.71 mmol, 71%).

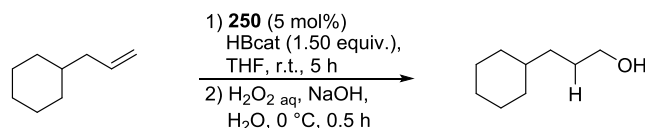
R<sub>f</sub> = 0.05 (pentane/diethyl ether, 80:20 v/v).

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.36-7.32 (m, 2H, ArH), 7.18-7.15 (m, 2H, ArH), 3.81 (app. q,  $J = 6.1$  Hz, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 2.81 (t,  $J = 6.6$  Hz, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.44 (br. t,  $J = 5.8$  Hz, 1H, OH), 1.31 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>).

$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ) 149.2 (C), 135.7 (C), 128.6 (CH), 125.3 (CH), 63.6 (CH<sub>2</sub>), 38.7 (CH<sub>2</sub>), 34.3 (C), 31.1 (CH<sub>3</sub>).

Data were in accordance with that previously reported.<sup>484</sup>

### 3-Cyclohexanepropan-1-ol (263)<sup>485</sup>



According to general procedure **H**, allylcyclohexane (0.124 g, 0.154 mL, 1.00 mmol) was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL). Following oxidation and flash column chromatography (conditions: silica, 15 g; 30 mm Ø; gradient pentane/diethyl ether, from 80:20 to 60:40 v/v over 10 column volumes) 3-cyclohexanepropan-1-ol was obtained (0.082 g, 0.58 mmol, 58%).

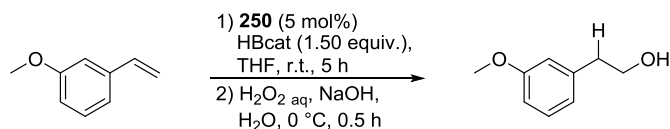
$R_{\text{f}} = 0.22$  (pentane/diethyl ether, 60:40 v/v).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 3.63-3.58 (m, 2H, CH<sub>2</sub>OH), 1.78-1.55 (m, 7H), 1.30-1.17 (m, 7H), 0.97-0.89 (m, 2H).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 63.2 (CH<sub>2</sub>), 37.5 (CH), 33.4 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>).

Data were in accordance with that previously reported.<sup>485</sup>

### 2-(3-Methoxyphenyl)ethan-1-ol (264)<sup>484</sup>



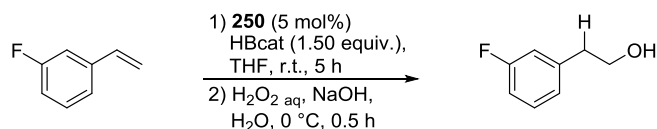
According to general procedure **H**, 3-methoxystyrene (0.134 g, 0.138 mL, 1.00 mmol) was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL).

Following oxidation, and addition of internal standard, 2-(3-methoxyphenyl)ethan-1-ol was obtained (44% by  $^1\text{H}$  NMR spectroscopy of crude product mixture).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.26-7.22 (m, 1H, ArH), 6.85-6.77 (m, 3H, ArH), 3.87 (t,  $J = 6.5$  Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.86 (t,  $J = 6.5$  Hz, 2H, Ar $\text{CH}_2$ ).

Data were in accordance with that previously reported.<sup>484</sup>

#### 2-(3-Fluorophenyl)ethan-1-ol (265)<sup>486</sup>

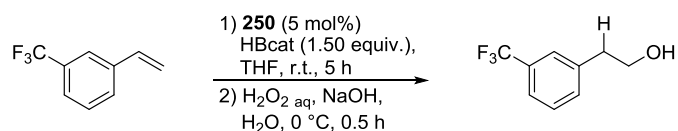


According to general procedure **H**, 3-fluorostyrene (0.122 g, 0.120 mL, 1.00 mmol) was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL). Following oxidation, and addition of internal standard, 2-(3-fluorophenyl)ethan-1-ol was obtained (44% by  $^1\text{H}$  NMR spectroscopy of crude product mixture).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.34-7.25 (m, 2H, ArH), 6.99-6.90 (m, 2H, ArH), 3.88 (t,  $J = 6.5$  Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.88 (t,  $J = 6.5$  Hz, 2H, Ar $\text{CH}_2$ ).

Data were in accordance with that previously reported.<sup>486</sup>

#### 2-(3-Trifluoromethylphenyl)ethan-1-ol (266)<sup>486</sup>



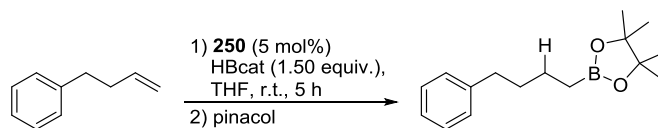
According to general procedure **H**, 3-trifluoromethylstyrene (0.172 g, 0.148 mL, 1.00 mmol) was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol) and bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) in anhydrous tetrahydrofuran (2 mL). Following oxidation, and addition of internal standard, 2-(3-trifluoromethylphenyl)ethan-1-ol was obtained (39% by  $^1\text{H}$  NMR spectroscopy of crude product mixture).

$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.60-7.40 (m, 4H, ArH), 3.94 (t,  $J = 6.5$  Hz, 2H,  $\text{CH}_2\text{OH}$ ), 2.94 (t,  $J = 6.5$  Hz, 2H, Ar $\text{CH}_2$ ).



Data were in accordance with that previously reported.<sup>486</sup>

#### 4-(1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**267**)<sup>18</sup>



According to general procedure **I**, 4-phenyl-1-butene (0.132 g, 0.150 mL, 1.00 mmol), was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol), bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) and pinacol (0.236 g, 2.00 mmol, 2.00 equivalents) in anhydrous tetrahydrofuran (2 mL). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 4-(1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained as a colourless oil (0.141 g, 0.54 mmol, 54%).

$R_f = 0.34$  (pentane/diethyl ether 95:5 v/v).

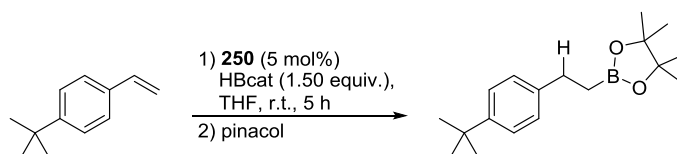
$\delta_H$  (500 MHz,  $CD_2Cl_2$ ) 7.29-7.25 (m, 2H, ArH), 7.21-7.15 (m, 3H, ArH), 2.60 (app. t,  $J = 7.8$  Hz, 2H, ArCH<sub>2</sub>), 1.64-1.58 (m, 2H, ArCH<sub>2</sub>CH<sub>2</sub>), 1.45-1.38 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>B), 1.21 (s, 12H, C(CH<sub>3</sub>)<sub>2</sub>), 0.76 (app. t,  $J = 7.8$  Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>B).

$\delta_C$  (126 MHz,  $CD_2Cl_2$ ) 143.6 (C), 128.9 (CH), 128.7 (CH), 126.0 (CH), 83.3 (C), 36.3 (CH<sub>2</sub>), 34.7 (CH<sub>2</sub>), 25.2 (CH<sub>3</sub>), 24.3 (CH<sub>2</sub>), 11.5 (br. s, CH<sub>2</sub>).

$\delta_B$  (160 MHz,  $CD_2Cl_2$ ) 33.9.

Data were in accordance with that previously reported.<sup>18</sup>

#### 2-[2-(4-*tert*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**268**)<sup>488</sup>



According to general procedure **I**, 4-*tert*-butylstyrene (0.132 g, 0.183 mL, 1.00 mmol), was reacted with catecholborane (0.180 g, 0.160 mL, 1.50 mmol), bis[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol) and pinacol (0.236 g, 2.00 mmol, 2.00 equivalents) in anhydrous tetrahydrofuran (2 mL). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 4-

(1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained as a colourless oil (0.141 g, 0.54 mmol, 54%).

$R_f = 0.32$  (pentane/diethyl ether 95:5 v/v).

$\delta_H$  (500 MHz,  $CD_2Cl_2$ ) 7.34-7.29 (m, 2H, ArH), 7.19-7.14 (m, 2H, ArH), 2.70 (app. t,  $J = 8.2$  Hz, 2H, ArCH<sub>2</sub>), 1.33 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.23 (s, 12H, C(CH<sub>3</sub>)<sub>2</sub>), 1.10 (app. t,  $J = 8.2$  Hz, CH<sub>2</sub>CH<sub>2</sub>B).

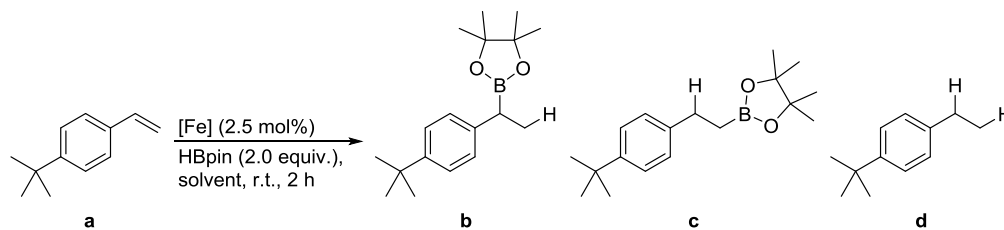
$\delta_C$  (126 MHz,  $CD_2Cl_2$ ) 148.9 (C), 142.1 (C), 128.1 (CH), 125.6 (CH), 83.6 (C), 34.8 (C), 31.7 (CH<sub>3</sub>), 30.0 (CH<sub>2</sub>), 25.2 (CH<sub>3</sub>), 13.8 (br. s, CH<sub>2</sub>).

$\delta_B$  (160 MHz,  $CD_2Cl_2$ ) 33.8.

Data were in accordance with that previously reported.<sup>488</sup>

## 5.13 HYDROBORATION REACTIONS WITH PINACOLBORANE: REACTION OPTIMISATION

**Table 5.13-1: Solvent Screen for hydroboration of 4-*tert*-butylstyrene**



Entry	[Fe] (mol%)	Solvent	Yield (%) <sup>a</sup>			
			<b>a</b>	<b>b</b>	<b>c</b>	<b>d</b>
1	FeBr <sub>2</sub> (2.5)	THF	93	-	-	7
2	<b>250</b> (1.0)	THF	90	-	-	9
3	<b>250</b> (1.0)	Toluene	87	-	-	11
4	<b>250</b> (1.0)	CH <sub>2</sub> Cl <sub>2</sub>	90	-	-	7
5	<b>253</b> (2.5)	THF	-	<b>6</b>	-	84
6	<b>253</b> (2.5)	Toluene	-	<b>7</b>	1	80
7	<b>253</b> (2.5)	Et <sub>2</sub> O	18	<b>3</b>	1	58
8	<b>253</b> (2.5)	CH <sub>2</sub> Cl <sub>2</sub>	55	-	-	5
9	<b>253</b> (2.5)	MeCN	77	-	-	9

<sup>a</sup>Yields determined by <sup>1</sup>H NMR spectroscopy of crude reaction mixtures relative to 1,3,5-trimethoxybenzene internal standard.

Pinacolborane (0.128 g, 0.145 mL, 1.00 mmol, 2.00 equivalents) was added to a solution of iron(II) complex (0.013 mmol, 0.025 equivalents) and 4-*tert*-butylstyrene (0.080 g, 0.092 mL, 0.50 mmol, 1.00 equivalent) in a solvent (2 mL). The resulting mixture was stirred at room temperature for 24 h, then water was added and the organic phase extracted with diethylether (3 × 10 mL) or dichloromethane (3 × 10 mL), dried over magnesium sulfate and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (0.017 g, 0.10 mmol, 0.20 equivalents) was added as an internal standard and the resulting mixture assessed by <sup>1</sup>H NMR spectroscopy and GCMS.

## 5.14 HYDROBORATION REACTIONS WITH PINACOLBORANE: REACTION MONITORING BY NMR SPECTROSCOPY

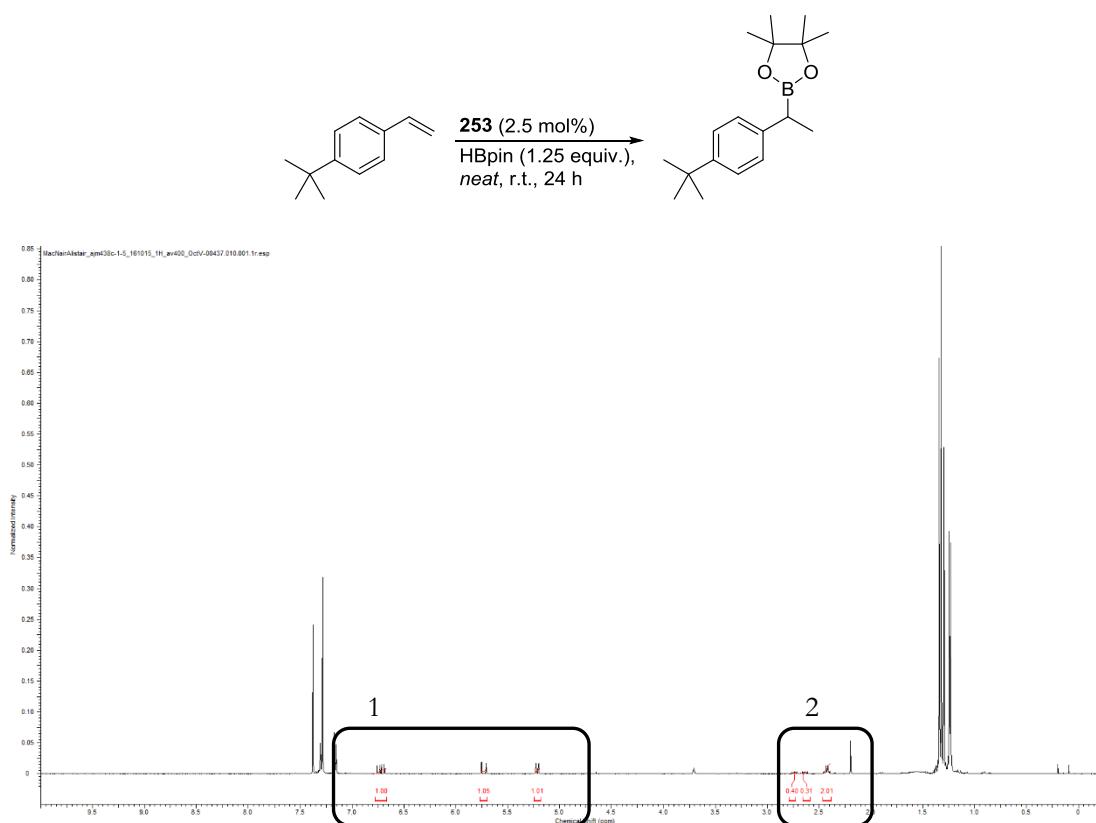
### General Procedure J: Hydroboration of alkenes with pinacolborane

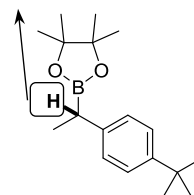
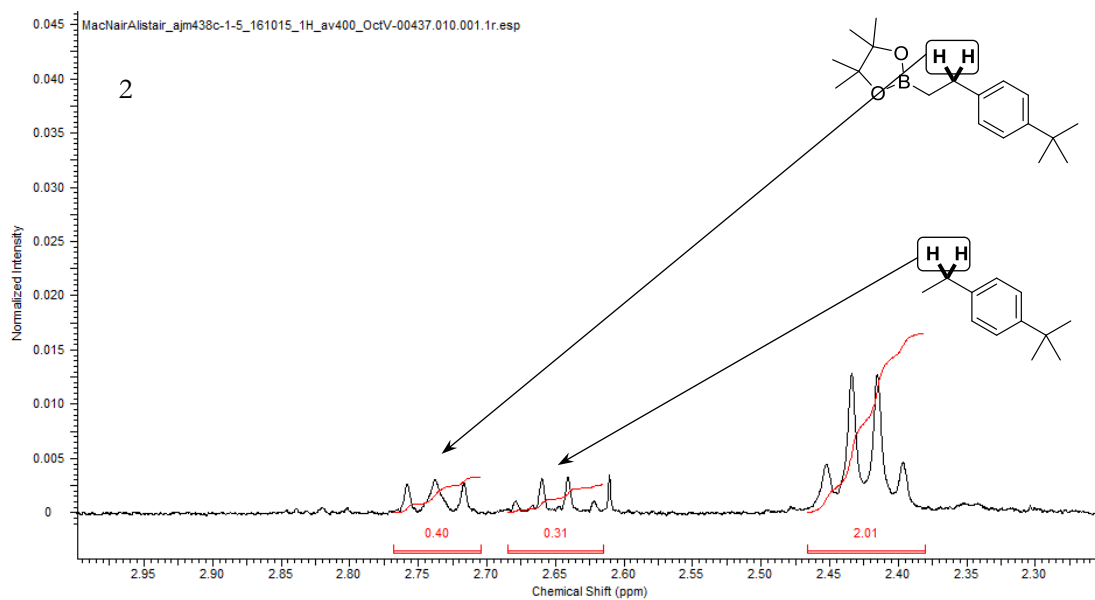
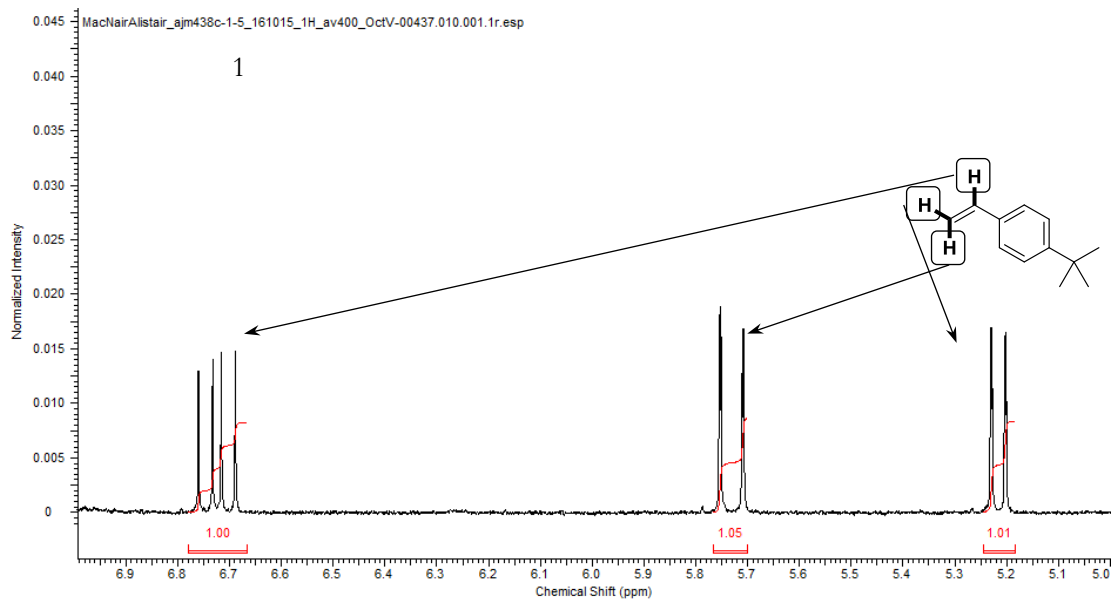
Reaction condition optimisation experiments, and initial substrate scope investigations, were monitored by  $^1\text{H}$  NMR spectroscopy according to the following protocol.

All reactions were carried out at room temperature ( $25 \pm 3\text{ }^\circ\text{C}$ ) in a Radley's carousel multiple position reactor under a purified nitrogen atmosphere.

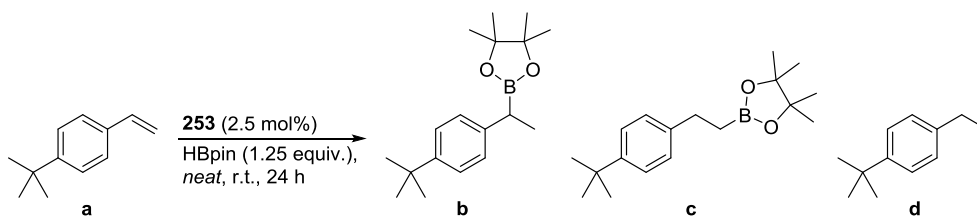
Pinacol borane (0.50 to 0.75 mmol, 1.00 to 1.50 equivalents) was added to bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.0025 mmol to 0.025 mmol, 0.005 to 0.05 equivalents), followed 15 s later by a styrene derivative (0.50 mmol, 1.00 equivalents). The resulting mixture was stirred at room temperature for up to 24 h. At pre-determined time points, aliquots ( $\leq 5\text{ }\mu\text{L}$ ) were removed from the reaction mixture, then diluted with *d*-chloroform, and assessed by  $^1\text{H}$  or  $^{11}\text{B}$  NMR spectroscopy by comparison to authentic samples.

### Example Analysis

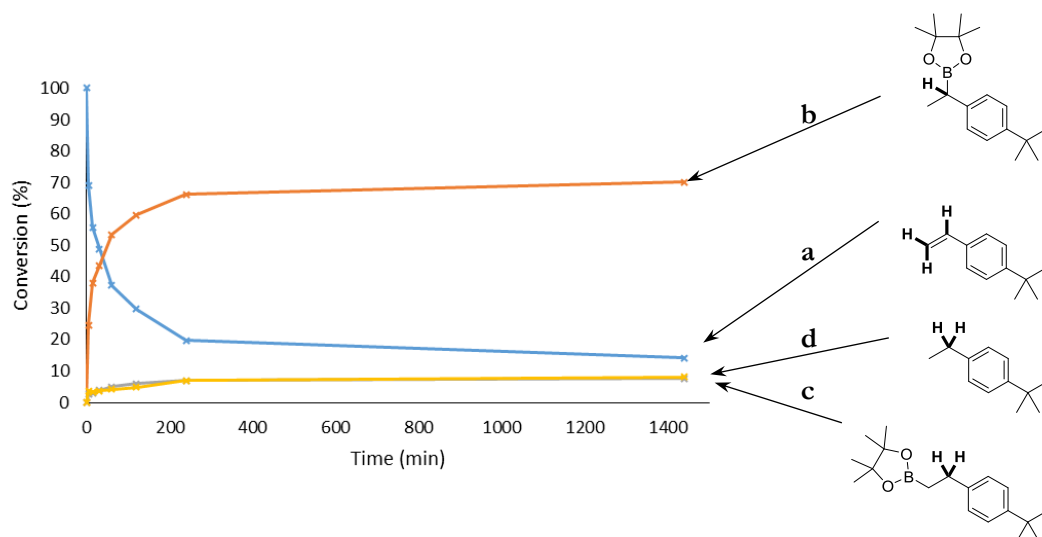
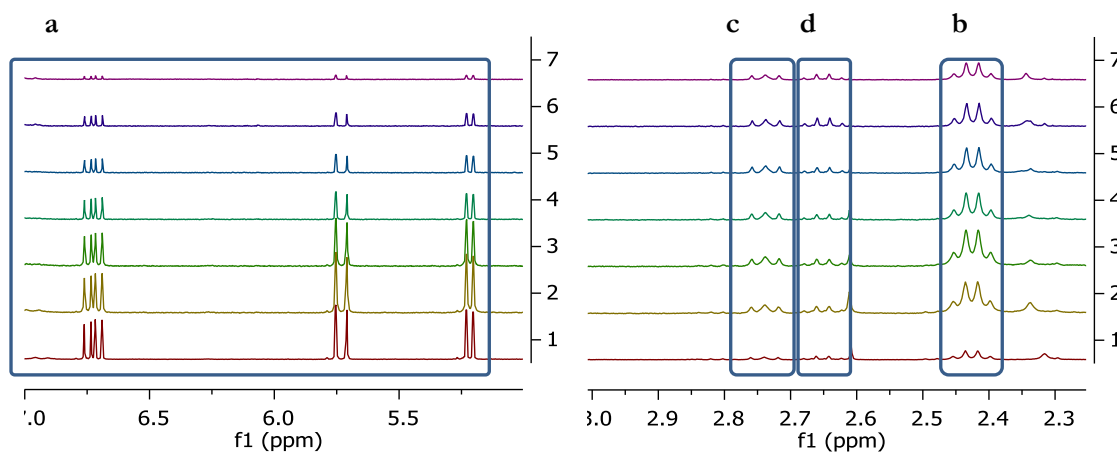




## Example run



Spectra number	Time (min)	4- <i>tert</i> -butylstyrene ( <b>a</b> ) (% remaining)	Branched hydroboration ( <b>b</b> ) (% conversion)	Linear hydroboration ( <b>c</b> ) (% conversion)	Hydrogenation ( <b>d</b> ) (% conversion)
1	5	69	25	2	4
2	15	56	38	3	3
3	30	49	44	4	4
4	60	37	53	5	4
5	120	30	60	6	5
6	240	20	66	7	7
7	1440	14	70	8	8



## 5.15 HYDROBORATION REACTIONS WITH PINACOLBORANE: ISOLATED PRODUCTS

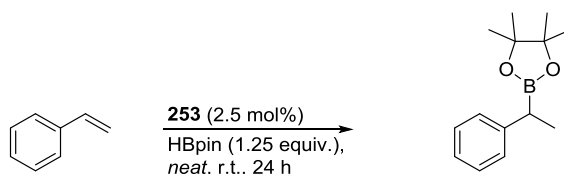
All reactions were carried out at room temperature ( $25 \pm 3$  °C) in a Radley's carousel multiple position reactor under a purified nitrogen atmosphere.

Pinacol borane was purchased from Flurochem and used as supplied.

### General Procedure K: Hydroboration of alkenes with pinacolborane

Pinacolborane (0.080 g, 0.092 mL, 0.63 mmol, 1.25 equivalents) was added to bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.008 g, 0.013 mmol, 0.025 equivalents), followed approximately 15 s later by an alkene (0.50 mmol, 1.00 equivalent). The resulting mixture was stirred at room temperature for 4 h, then diluted with *d*-chloroform and assessed by  $^1\text{H}$  NMR. The hydroboration product was then isolated following flash column chromatography (conditions: silica, 7-15 g; 30 mm Ø; solvent system – petroleum spirit or pentane/diethyl ether, 95:5 over 5 column volumes).

#### 2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (194)<sup>489</sup>



According to general procedure **K**, styrene (0.052 g, 0.057 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 7 g; 30 mm Ø; petroleum spirit /diethyl ether, 95:5 v/v over 5 column volumes) 2-(1-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.094 g, 0.41 mmol, 81%) was obtained as a colourless oil. A small portion of the boronic ester product was oxidised with basic hydrogen peroxide and analysed by chiral HPLC.

$R_f = 0.29$  (petroleum spirit:diethyl ether, 95:5 v/v).

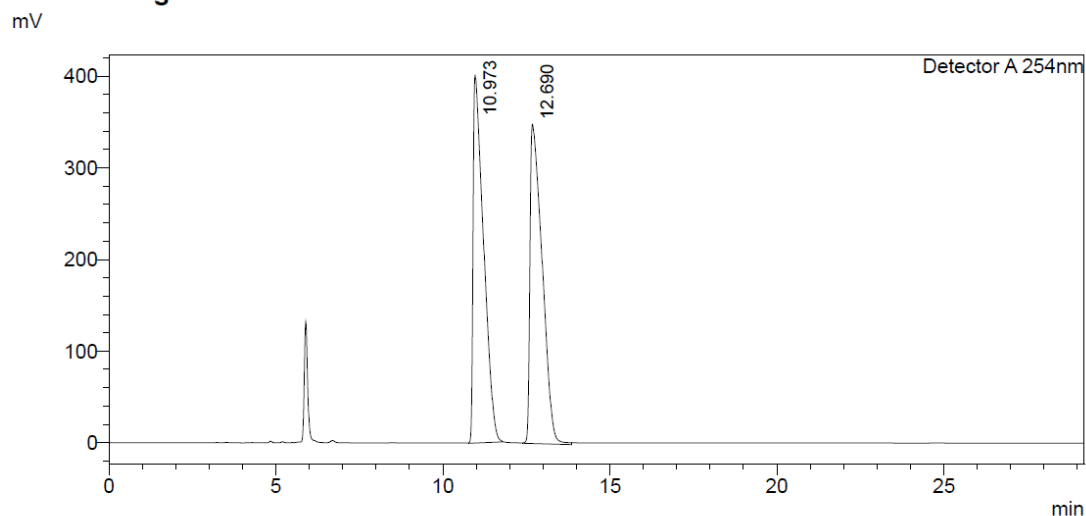
$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.31-7.23 (m, 4H, ArH), 7.16 (m, 1H, ArH), 2.46 (q,  $J = 7.5$  Hz, 1H, CH), 1.36 (d,  $J = 7.5$  Hz, 3H,  $\text{CHCH}_3$ ), 1.24 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.23 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CDCl}_3$ ) 145.0 (C), 128.3 (CH), 127.8 (CH), 125.1 (CH), 83.3 (C), 24.8 (CH), 24.6 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 17.1 (CH<sub>3</sub>).

$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.6.

HPLC conditions: hexane/*i*PrOH, 95:5 v/v; 0.5 mL/min ;  $R_f$ : 11.0 min (49.6%), 12.6 min (50.4%).<sup>490</sup> Assigned by comparison with an authentic sample of phenylethan-1-ol.

#### <Chromatogram>



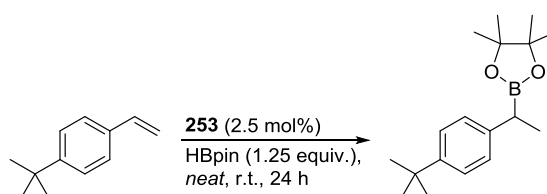
#### <Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10.973	8693081	401020	49.581		M	
2	12.690	8840170	348294	50.419		M	
Total		17533251	749314				

Data were in accordance with that previously reported.<sup>489</sup>

#### 2-[1-(4-*tert*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (271)



According to general procedure **K**, 4-*tert*-butylstyrene (0.080 g, 0.092 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.50 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum spirit /diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-*tert*-butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.094 g, 0.33 mmol, 65%) was obtained as a colourless oil.

$R_f$  = 0.36 (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\max}$ /cm<sup>-1</sup> (neat): 2963, 1458 (br), 1352, 1319, 1269, 1213, 1143, 1062, 1016, 964, 847, 829.



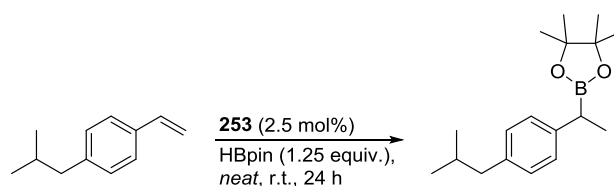
$\delta_{\text{H}}$  (500 MHz,  $\text{CDCl}_3$ ) 7.30-7.27 (m, 2H, ArH), 7.17-7.13 (m, 2H, ArH), 2.41 (q,  $J = 7.5$  Hz, 1H, CH), 1.32 (d,  $J = 7.5$  Hz, 3H,  $\text{CHCH}_3$ ), 1.31 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 1.23 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.22 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 147.6 (C), 141.7 (C), 127.4 (CH), 125.2 (CH), 83.2 (C), 34.3 (C), 31.5 (CH<sub>3</sub>), 24.8 (CH), 24.7 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 17.2 (CH<sub>3</sub>).

$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.7.

HRMS (ESI) Exact mass calculated for  $\text{C}_{18}\text{H}_{30}\text{O}_2^{11}\text{B}_1$   $[\text{M}+\text{H}]^+$ : 289.23334, found: 289.23200.

## 2-[1-(4-*iso*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (272)



According to general procedure **K**, 4-*iso*-butylstyrene (0.080 g, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 7 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-*iso*-butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.104 g, 0.36 mmol, 72%) was obtained as a colourless oil.

$R_f = 0.34$  (pentane:diethyl ether, 95:5 v/v).

$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 2955, 1456, 1371, 1352, 1319, 1143, 847.

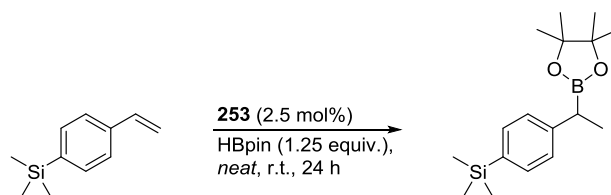
$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.13-7.10 (m, 2H, ArH), 7.09-7.05 (m, 2H, ArH), 2.46 (d,  $J = 7.1$  Hz, 2H, ArCH<sub>2</sub>), 2.39 (q,  $J = 7.6$  Hz, 1H, ArCH), 1.87 (app. non.,  $J = 6.6$  Hz, 1H,  $\text{CH}_2\text{CH}(\text{CH}_3)_2$ ), 1.31 (m,  $J = 7.6$  Hz, 2H,  $\text{CHCH}_3$ ), 1.24 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.23 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 0.93 (d,  $J = 6.6$  Hz, 6H,  $\text{CH}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ) 142.4 (C), 138.3 (C), 129.0 (CH), 127.4 (CH), 83.2 (C), 44.9 (CH<sub>2</sub>), 30.2 (CH), 24.6 (CH), 24.4 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>).

$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.6.

Data were in accordance with that previously reported.<sup>463</sup>

## 2-[1-(4-Trimethylsilylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (273)



According to general procedure **K**, 4-trimethylsilylstyrene (0.088 g, 0.099 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 12 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-trimethylsilylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.059 g, 0.19 mmol, 38%) was obtained as a colourless oil.

$R_f$  = 0.36 (pentane:diethyl ether, 95:5 v/v).

$\nu_{\max}$ /cm<sup>-1</sup> (neat): 2978, 1440, 1325, 1247, 1143 981, 840.

$\delta_H$  (600 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.47 (m, 2H, ArH), 7.22-7.18 (m, 2H, ArH), 2.41 (q,  $J$  = 7.5 Hz, 1H, ArCH), 1.33 (d,  $J$  = 7.5 Hz, 3H, CHCH<sub>3</sub>), 1.25 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.24 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 0.29 (s, 9H, Si(CH<sub>3</sub>)<sub>3</sub>).

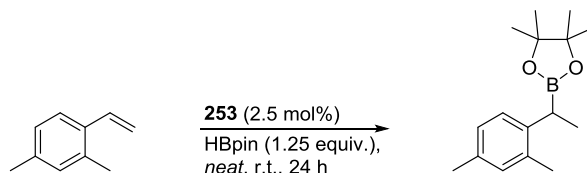
$\delta_C$  (151 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 146.1 (C), 136.3 (C), 133.4 (CH), 127.3 (CH), 83.3 (C), 24.6 (CH), 24.4 (CH<sub>3</sub>), 16.9 (CH<sub>3</sub>), -1.42 (CH<sub>3</sub>).

$\delta_B$  (160 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 33.6.

$\delta_{Si}$  (99 MHz, CD<sub>2</sub>Cl<sub>2</sub>) -4.61.

HRMS (ESI) Exact mass calculated for C<sub>17</sub>H<sub>29</sub>BO<sub>2</sub>SiNa [M+Na]<sup>+</sup>: 327.19221, found: 327.19190.

## 2-[1-(2,4-Dimethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (272)



According to general procedure **K**, 2,4-dimethylstyrene (0.066 g, 0.073 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash

column chromatography (conditions: silica, 10 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(2,4-dimethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.045 g, 0.17 mmol, 35%) was obtained as a colourless oil in a 5:1 mixture with the linear isomer.

$R_f = 0.22$  (pentane:diethyl ether, 95:5 v/v).

$\nu_{\max}/\text{cm}^{-1}$  (neat): 2976, 1454, 1371, 1352, 1317, 1143, 845.

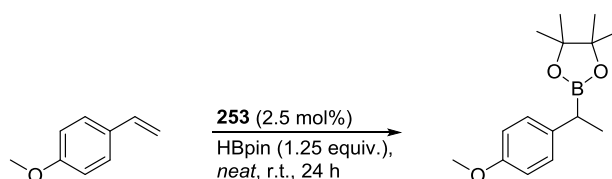
$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.02-6.99 (m, 1H, ArH), 6.93-6.90 (m, 2H, ArH), 2.48 (q,  $J = 7.5$  Hz, 1H, ArCH), 2.26 (s, 3H, ArCH<sub>3</sub>), 2.22 (s, 3H, ArCH<sub>3</sub>), 1.25 (d,  $J = 7.5$  Hz, CHCH<sub>3</sub>), 1.20 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.19 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ) 140.5 (C), 135.4 (C), 134.3 (C), 130.8 (CH), 127.0 (CH), 126.3 (CH), 83.2 (C), 24.6 (CH), 24.4 (CH<sub>3</sub>), 24.4 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>), 19.5 (CH<sub>3</sub>), 16.0 (CH<sub>3</sub>).

$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.7.

HRMS (ESI) Exact mass calculated for  $\text{C}_{16}\text{H}_{26}\text{BO}_2$   $[\text{M}+\text{H}]^+$ : 261.20204, found: 261.20340.

## 2-[1-(4-Methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**277**)<sup>491</sup>



According to general procedure **K**, 4-methoxystyrene (0.067 g, 0.066 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 12 g; 30 mm Ø; petroleum spirit/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.076 g, 0.29 mmol, 58%) was obtained as a colourless oil.

$R_f = 0.16$  (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\max}/\text{cm}^{-1}$  (neat): 2976, 1508, 1456, 1371, 1352, 1317, 1242, 1143, 1038, 845, 827, 739, 673.

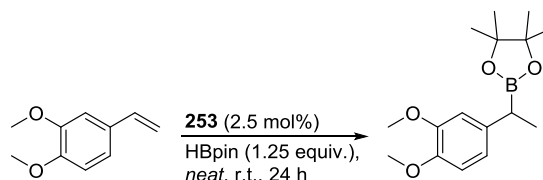
$\delta_{\text{H}}$  (600 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.09 (dt,  $J = 8.7, 2.5$  Hz, 2H, ArH), 6.80 (dt,  $J = 8.7, 2.5$  Hz, 2H, ArH), 3.76 (s, 3H, OCH<sub>3</sub>), 2.32 (q,  $J = 7.5$  Hz, 1H, CHCH<sub>3</sub>), 1.26 (d,  $J = 7.5$  Hz, 3H, CHCH<sub>3</sub>), 1.20 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.19 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_C$  (151 MHz,  $CD_2Cl_2$ ) 157.6 (C), 137.3 (C), 128.6 (CH), 113.6 (CH), 83.2 (C), 55.1 ( $CH_3$ ), 24.6 (CH), 24.4 ( $CH_3$ ), 17.1 ( $CH_3$ ).

$\delta_B$  (160 MHz,  $CD_2Cl_2$ ) 33.6.

Data were in accordance with that previously recorded.<sup>491</sup>

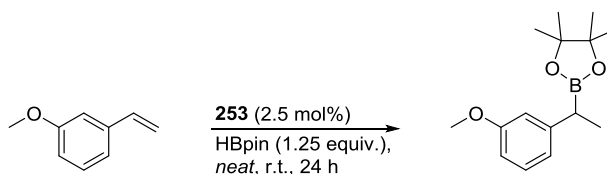
### 2-[1-(3,4-Dimethoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (278)



According to general procedure **K**, 3,4-dimethoxystyrene (0.082 g, 0.076 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). 2-[1-(3,4-dimethoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained (45% conversion by  $^1H$  NMR spectroscopy). The resultant product decomposed during flash column chromatography.

$\delta_H$  (400 MHz,  $CDCl_3$ ) 6.98 (d,  $J$  = 2.0 Hz, 1H, ArH), 6.96 (dd,  $J$  = 8.2, 2.0 Hz, 1H, ArH), 6.84 (d,  $J$  = 8.2 Hz, 1H, ArH), 3.87 (s, 3H,  $OCH_3$ ), 3.85 (s, 3H,  $OCH_3$ ), 2.38 (q,  $J$  = 7.5 Hz, 1H,  $CHCH_3$ ), 1.32 (d,  $J$  = 7.5 Hz, 3H,  $CHCH_3$ ), 1.23 (s, 6H,  $C(CH_3)_2$ ), 1.22 (s, 6H,  $C(CH_3)_2$ ).

### 2-[1-(3-Methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (279)<sup>489</sup>



According to general procedure **K**, 3-methoxystyrene (0.067 g, 0.069 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum spirit/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(3-methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.063 g, 0.24 mmol, 48%) was isolated as a colourless oil (mixture containing 5% linear isomer by  $^1H$  NMR spectroscopy).

$R_f$  = 0.13 (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 2976, 1599, 1582, 1485, 1456, 1371, 1348, 1319, 1250, 1135, 1045, 858, 777, 708.

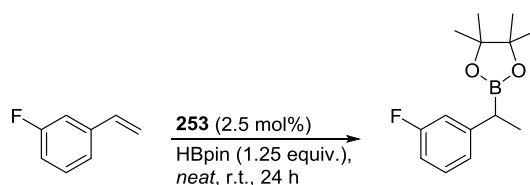
$\delta_{\text{H}}$  (600 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.17 (app. t,  $J = 7.9$  Hz, 1H, ArH), 6.79-6.76 (m, 1H, ArH), 6.75-6.73 (m, 1H, ArH), 6.68 (ddd,  $J = 8.2, 2.6, 0.9$  Hz, 1H, ArH), 3.78 (s, 3H,  $\text{OCH}_3$ ), 2.38 (q,  $J = 7.5$  Hz, 1H,  $\text{CHCH}_3$ ), 1.30 (d,  $J = 7.5$  Hz, 3H,  $\text{CHCH}_3$ ), 1.22 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.21 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ).

$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ) 159.7 (C), 147.0 (C), 129.1 (CH), 120.2 (CH), 113.5 (CH), 110.4 (CH), 83.3 (C), 55.0 ( $\text{CH}_3$ ), 24.6 (C), 24.4 ( $\text{CH}_3$ ), 16.8 ( $\text{CH}_3$ ).

$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.5.

Data were in accordance with that previously recorded.<sup>489</sup>

### 2-[1-(3-Fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**283**)



According to general procedure **K**, 3-fluorostyrene (0.061 g, 0.060 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum spirit/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(3-fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.113 g, 0.45 mmol, 90%) was obtained as a colourless oil.

$R_f = 0.24$  (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\text{max}}/\text{cm}^{-1}$  (neat): 2978, 1612, 1585, 1483, 1447, 1348, 1323, 1265, 1242, 1143, 984, 964, 912, 862, 841.

$\delta_{\text{H}}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.22 (ddd,  $J = 7.9, 7.9, 6.3$  Hz, 1H, ArH), 6.99-6.96 (m, 1H, ArH), 6.91 (ddd,  $J = 10.6, 2.0, 2.0$  Hz, 1H, ArH), 6.85-6.80 (m, 1H, ArH), 2.42 (q,  $J = 7.5$  Hz, 1H,  $\text{CHCH}_3$ ), 1.29 (d,  $J = 7.5$  Hz, 3H,  $\text{CHCH}_3$ ), 1.20 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ), 1.19 (s, 6H,  $\text{C}(\text{CH}_3)_2$ ).

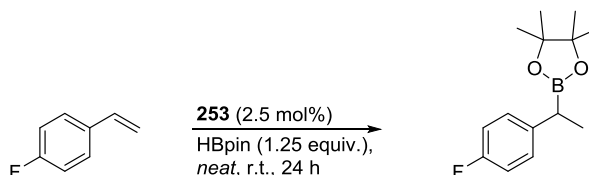
$\delta_{\text{C}}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ) 163.1 (d,  $J = 244.3$  Hz, C), 148.2 (d,  $J = 7.5$  Hz, C), 129.5 (d,  $J = 8.5$  Hz, CH), 123.5 (d,  $J = 2.5$  Hz, CH), 114.4 (d,  $J = 21.4$  Hz, CH), 111.7 (d,  $J = 20.9$  Hz, CH), 83.5 (C), 24.6 (CH), 24.4 ( $\text{CH}_3$ ), 16.5 ( $\text{CH}_3$ ).

$\delta_B$  (160 MHz,  $CD_2Cl_2$ ) 33.4.

$\delta_F$  (471 MHz,  $CD_2Cl_2$ ) -114.83 (ddd,  $J = 9.7, 9.7, 6.4$  Hz).

HRMS (ESI) Exact mass calculated for  $C_{14}H_{21}O_2^{11}B_1F_1$   $[M+H]^+$ : 251.16132, found: 251.16090.

**2-[1-(4-Fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284)**<sup>489</sup>



According to general procedure **K**, 4-fluorostyrene (0.061 g, 0.060 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2N-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 15 g; 30 mm Ø; petroleum spirit/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.104 g, 0.42 mmol, 83%) was obtained as a colourless oil.

$R_f = 0.38$  (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{max}/cm^{-1}$  (neat): 2978, 1506, 1456, 1352, 1321, 1217, 1142, 843, 833, 740, 673.

$\delta_H$  (600 MHz,  $CD_2Cl_2$ ) 7.22-7.17 (m, 2H, ArH), 7.02-6.97 (m, 2H, ArH), 2.43 (q,  $J = 7.5$  Hz, 1H, CH), 1.32 (d,  $J = 7.5$  Hz, 3H, CHCH<sub>3</sub>), 1.24 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.23 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_C$  (126 MHz,  $CD_2Cl_2$ ) 161.4 (d,  $J = 242.4$  Hz, C), 141.7 (d,  $J = 3.0$  Hz, C), 129.7 (d,  $J = 7.5$  Hz, CH), 115.4 (d,  $J = 20.9$  Hz, CH), 84.0 (C), 25.2 (C), 25.0 (CH<sub>3</sub>), 25.0 (CH<sub>3</sub>), 17.6 (CH<sub>3</sub>).

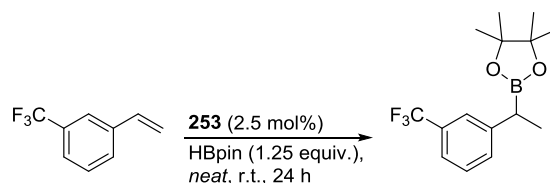
$\delta_B$  (160 MHz,  $CD_2Cl_2$ ) 33.5.

$\delta_F$  (471 MHz,  $CD_2Cl_2$ ) -119.8 (tt,  $J = 9.0, 5.5$  Hz)

HRMS (ESI) Exact mass calculated for  $C_{14}H_{21}O_2^{11}B_1F_1$   $[M+H]^+$ : 251.16132, found: 251.16140.

Data were in accordance with that previously reported.<sup>489</sup>

## 2-[1-(3-Trifluoromethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (285)



According to general procedure **K**, 4-methoxystyrene (0.086 g, 0.074 mL, 0.50 mmol) was reacted with pinacolborane (0.080 g, 0.091 mL, 0.63 mmol) and bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol). Following flash column chromatography (conditions: silica, 12 g; 30 mm Ø; petroleum spirit/diethyl ether, 95:5 v/v over 5 column volumes) 2-[1-(4-*fluorophenyl*)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.097 g, 0.32 mmol, 64%) was obtained as a colourless oil.

$R_f = 0.19$  (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\max}/\text{cm}^{-1}$  (neat): 2978, 1329, 1161, 1124, 1074, 851, 800, 702.

$\delta_{\text{H}}$  (600 MHz,  $\text{CD}_2\text{Cl}_2$ ) 7.46 (br. s, 1H, ArH), 7.44–7.37 (m, 3H, ArH), 2.49 (q,  $J = 7.5$  Hz, 1H, CHCH<sub>3</sub>), 1.33 (d,  $J = 7.5$  Hz, 3H, CHCH<sub>3</sub>), 1.20 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.19 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_{\text{C}}$  (151 MHz,  $\text{CD}_2\text{Cl}_2$ ) 146.4 (C), 131.4 (CH), 130.2 (q,  $J = 31.6$  Hz, C), 128.6 (CH), 124.5 (q,  $J = 271.8$  Hz, CF<sub>3</sub>), 124.4 (q,  $J = 3.9$  Hz, CH), 121.8 (q,  $J = 3.9$  Hz, CH), 83.5 (C), 24.6 (CH), 24.4 (CH<sub>3</sub>), 16.5 (CH<sub>3</sub>).

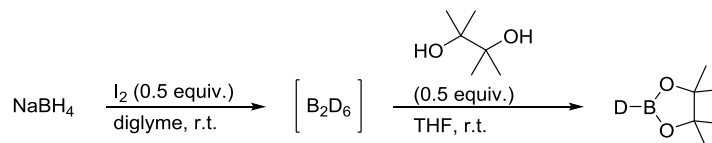
$\delta_{\text{B}}$  (160 MHz,  $\text{CD}_2\text{Cl}_2$ ) 33.4.

$\delta_{\text{F}}$  (471 MHz,  $\text{CD}_2\text{Cl}_2$ ) -62.9.

HRMS (ESI) Exact mass calculated for C<sub>15</sub>H<sub>20</sub>O<sub>2</sub><sup>11</sup>B<sub>1</sub>F<sub>3</sub><sup>23</sup>Na [M+<sup>23</sup>Na]<sup>+</sup>: 323.14007, found: 323.13970.

## 5.16 HYDROBORATION REACTIONS WITH PINACOLBORANE: DEUTERIUM LABELLING EXPERIMENTS

*d*<sub>1</sub>-Pinacolborane<sup>492</sup>



Synthesised according to modified literature procedures.<sup>492</sup>

*Safety Concern:* This reaction liberates pyrophoric and toxic polydeuterated diborane gas, this should be quenched in a controlled manner. Additionally flammable D<sub>2</sub> gas is liberated.

The reaction and purification procedures were performed in Schlenk glassware under a purified nitrogen atmosphere.

A solution of iodine (5.080 g, 20.00 mmol) in diethylene glycol dimethyl ether (20 mL) was added dropwise at room temperature over 3 h to a solution of sodium borodeuteride (1.674 g, 40.00 mmol) in diethylene glycol dimethyl ether (20 mL). The resulting gas was vented, through a plastic cannula, into a solution of pinacol (2.360 g, 20.00 mmol) in tetrahydrofuran (10 mL). After completion of addition of the iodine solution, a stream of nitrogen gas was applied to the diethylene glycol dimethyl ether solution for 2 h, such that any residual gasses were bubbled through the tetrahydrofuran solution. Volatiles were removed from resulting tetrahydrofuran solution of *d*<sub>1</sub>-pinacolborane *in vacuo* (200 mbar, 30-40 °C). Following vacuum distillation (50 mbar, 40 °C), *d*<sub>1</sub>-pinacolborane was isolated (0.526 g, 4.08 mmol, 20%).

δ<sub>H</sub> (500 MHz, C<sub>6</sub>D<sub>6</sub>) 0.99 (s, 12H, CH<sub>3</sub>).

δ<sub>C</sub> (126 MHz, C<sub>6</sub>D<sub>6</sub>) 83.4 (C), 25.3 (CH<sub>3</sub>).

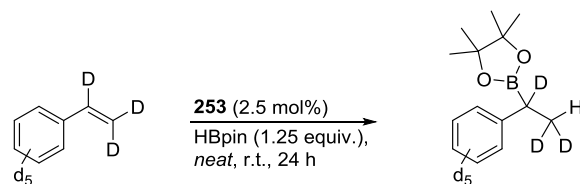
δ<sub>B</sub> (160 MHz, C<sub>6</sub>D<sub>6</sub>) 28.4 (br. s).

δ<sub>D</sub> (77 MHz, C<sub>6</sub>H<sub>6</sub>) 5.12-3.71 (br. m).

Data were in accordance with that previously reported.<sup>492</sup>



**2-[1-(*d*<sub>5</sub>-Phenyl)-1-*d*<sub>1</sub>-2-*d*<sub>2</sub>-ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*d*<sub>8</sub>-194)**



Pinacolborane (0.080 g, 0.091 mL, 0.63 mmol, 1.25 equivalents) was added to an bis{1-[mesityl]-3-[(*J*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol, 0.025 equivalents), followed approximately 15 s later by *d*<sub>8</sub>-styrene (0.052 g, 0.057 mL, 0.50 mmol, 1.00 equivalent). The resulting mixture was stirred at room temperature for 4 h, then diluted with chloroform and assessed by <sup>2</sup>H NMR spectroscopy. Following flash column chromatography (conditions: silica, 7 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 2-(1-(*d*<sub>5</sub>-Phenyl)-1-*d*<sub>1</sub>-2-*d*<sub>2</sub>-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained as a colourless oil (0.082 g, 0.34 mmol, 68%).

R<sub>f</sub> = 0.29 (petroleum spirit:diethyl ether, 95:5 v/v).

ν<sub>max</sub>/cm<sup>-1</sup> (neat): 2978, 1371, 1346, 1315, 1271, 1146, 860.

δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.34-1.30 (br. m, 1H, CDCl<sub>2</sub>H), 1.24 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.22 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

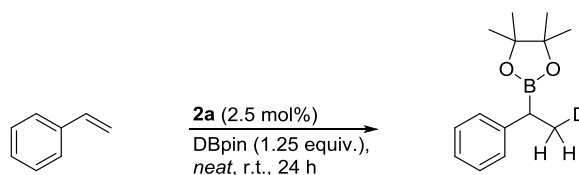
δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 144.8 (C), 127.8 (t, *J* = 24.2 Hz, CD), 127.3 (t, *J* = 23.7 Hz, CD), 124.5 (t, *J* = 24.2 Hz, CD), 83.3 (C), 24.8 (CD), 24.6 (CH<sub>3</sub>), 24.6 (CH<sub>3</sub>), 16.3 (quint., *J* = 19.3 Hz, CD<sub>2</sub>H).

δ<sub>B</sub> (160 MHz, CDCl<sub>3</sub>) 33.6.

δ<sub>D</sub> (77 MHz, CHCl<sub>3</sub>) 7.31 (br. s), 7.28 (br. s), 7.19 (br. s), 2.42 (br. s), 1.32 (br. d, *J* = 1.78 Hz).

HRMS (ESI) Exact mass calculated for C<sub>14</sub>H<sub>14</sub><sup>2</sup>H<sub>8</sub><sup>11</sup>BO<sub>2</sub> [M+H]<sup>+</sup>: 241.22095, found: 241.22230.

**2-(1-Phenyl-2-*d*<sub>1</sub>-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*d*<sub>1</sub>-194)**



The reaction was performed in a glovebox under a purified argon atmosphere.

*d*<sub>1</sub>-Pinacolborane (0.081 g, 0.63 mmol, 1.25 equivalents) was added to an bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol, 0.025 equivalents), followed approximately 15 s later by styrene (0.052 g, 0.057 mL, 0.50 mmol, 1.00 equivalent). The resulting mixture was stirred at room temperature for 4 h, then diluted with *d*<sub>2</sub>-dichloromethane and assessed by <sup>1</sup>H NMR spectroscopy. Following flash column chromatography (conditions: silica, 7 g; 30 mm Ø; pentane/diethyl ether, 95:5 v/v over 5 column volumes) 2-(1-phenyl-2-*d*<sub>1</sub>-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained in an approximately 3:1 mixture with 2-(1-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a colourless oil (0.054 g, 0.23 mmol, 46%).

*R*<sub>f</sub> = 0.29 (petroleum spirit:diethyl ether, 95:5 v/v).

$\nu_{\text{max}}$ /cm<sup>-1</sup> (neat): 2978, 1674, 1473, 1449, 1371, 1327, 1144, 982, 851, 754, 698, 670.

$\delta_{\text{H}}$  (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 7.31-7.26 (m, 2H, ArH<sub>m</sub>), 7.23-7.20 (m, 2H, ArH<sub>o</sub>), 7.16 (tt, *J* = 7.3, 1.3 Hz, 1H, ArH<sub>p</sub>), 2.42 (app. t, *J* = 7.4 Hz, 1H, ArCH), 1.35-1.30 (m, 2.4H, 3:1 mixture of CH<sub>3</sub> and CH<sub>2</sub>D), 1.24 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>), 1.23 (s, 6H, C(CH<sub>3</sub>)<sub>2</sub>).

$\delta_{\text{C}}$  (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 146.0 (C), 128.8 (CH), 128.4 (CH), 125.6 (CH), 83.9 (C), 25.0 (CH<sub>3</sub>), 17.4 (s, CH<sub>3</sub>, from protonated product), 17.2 (t, *J* = 19.5 Hz, CH<sub>2</sub>D from mono-deuterated product).

$\delta_{\text{B}}$  (160 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 33.6.

$\delta_{\text{D}}$  (77 MHz, CH<sub>2</sub>Cl<sub>2</sub>) 1.37-1.25 (br. m).

HRMS (ESI) Exact mass calculated for C<sub>14</sub>H<sub>21</sub><sup>2</sup>H<sub>1</sub>O<sub>2</sub><sup>11</sup>B<sub>1</sub> [M+H]<sup>+</sup>: 234.17701, found: 234.17660.

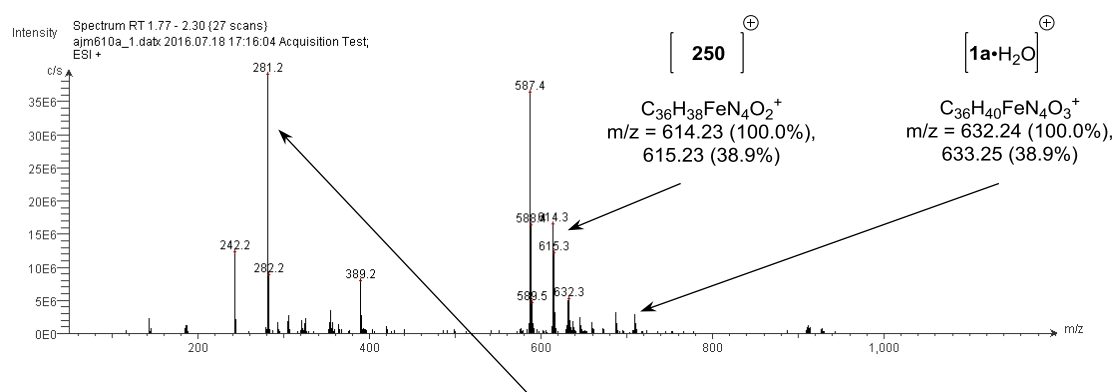
## 5.17 HYDROBORATION REACTIONS: REACTION MONITORING WITH ESI-MS

All reactions were carried out at room temperature ( $25 \pm 3$  °C) in a glovebox under a purified argon atmosphere.

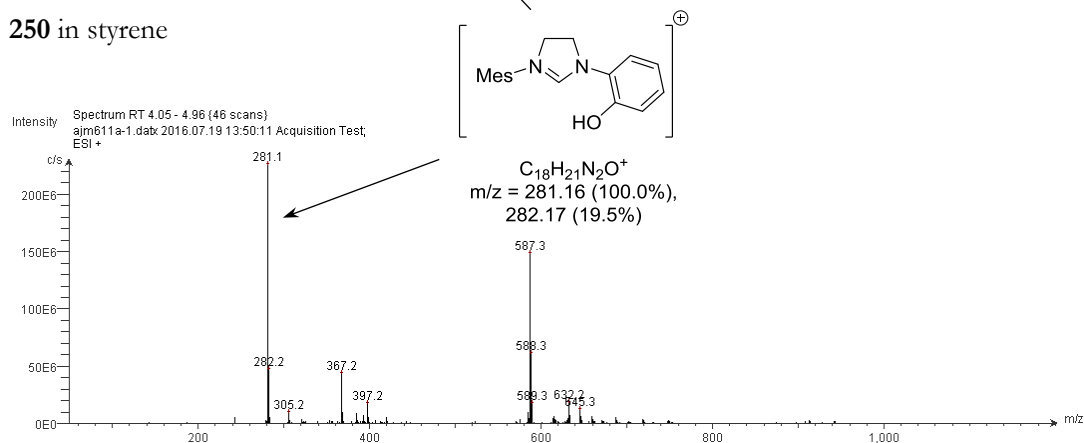
### Complex 250

Peak at  $m/z = 587.4$  is formed on ionisation under ESI<sup>+</sup> conditions. This peak is not observed in the same sample under EI conditions.

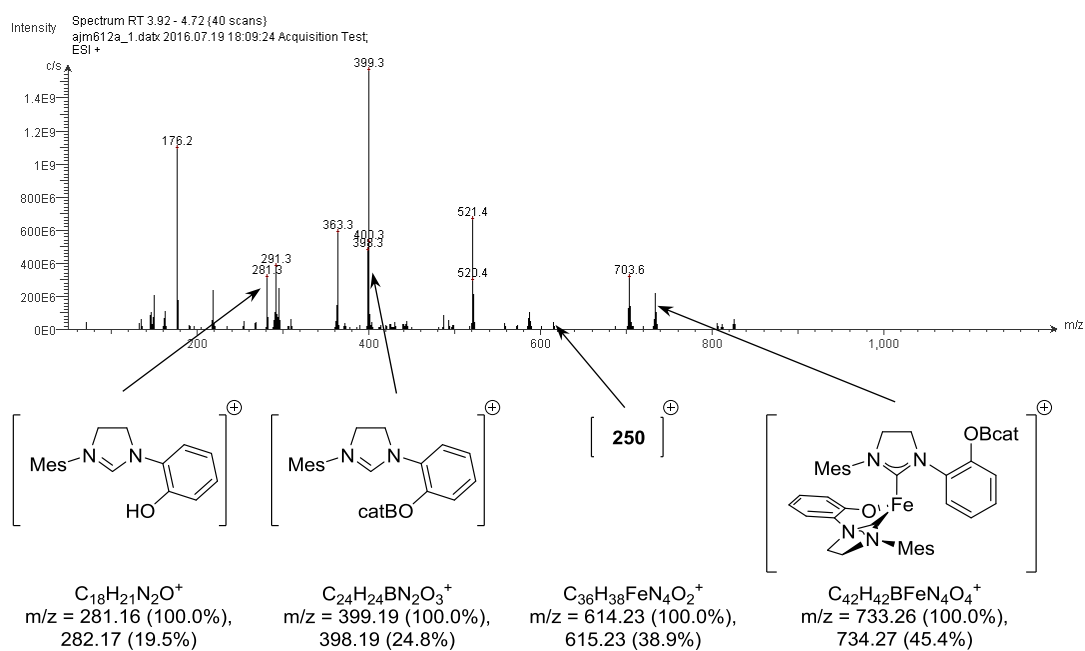
### 250 in tetrahydrofuran



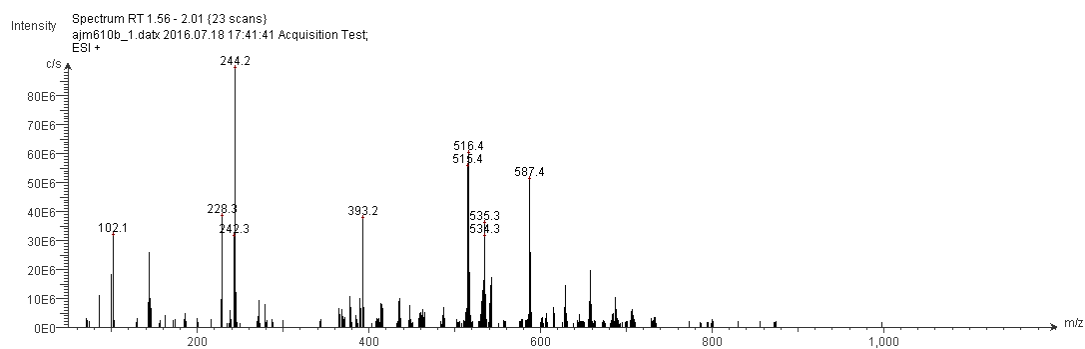
### 250 in styrene



## 250 in HBcat

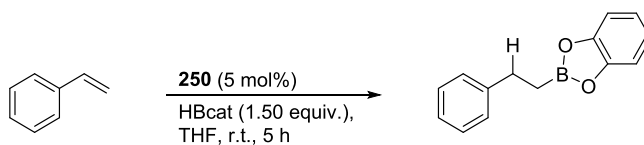


## 250 in HBpin

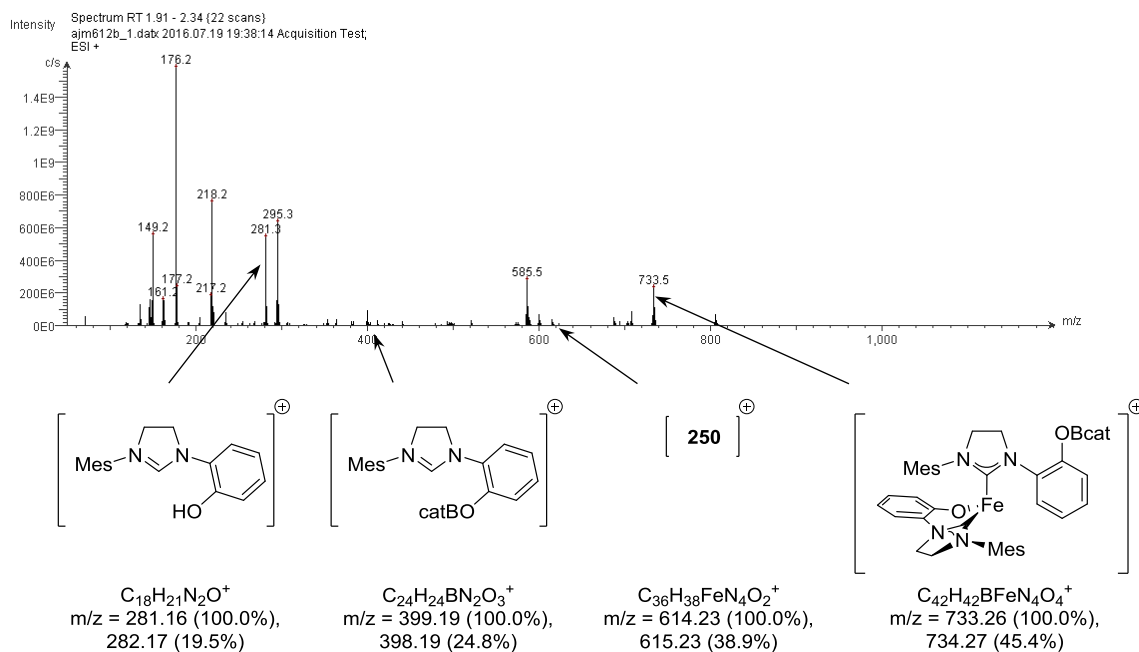


## Complex 250: Hydroboration of alkenes with catecholborane

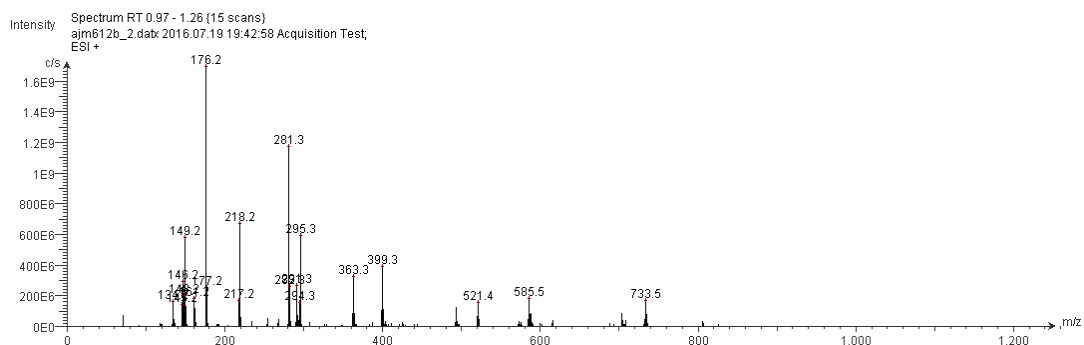
Catecholborane (0.090 g, 0.80 mL, 0.75 mmol, 1.50 equivalents) was added in one portion to a mixture of an alkene (0.50 mmol, 1.00 equivalent) and bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.015 g, 0.025 mmol, 0.05 equivalents) in anhydrous tetrahydrofuran (1 mL). Aliquots (*ca.* 5  $\mu$ L) were removed from the reaction mixture and analysed by ESI-MS.



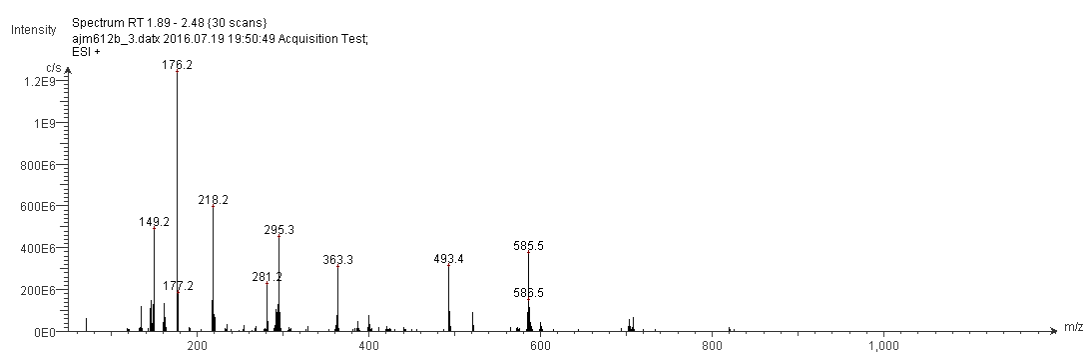
Aliquot, immediately after HBcat addition:



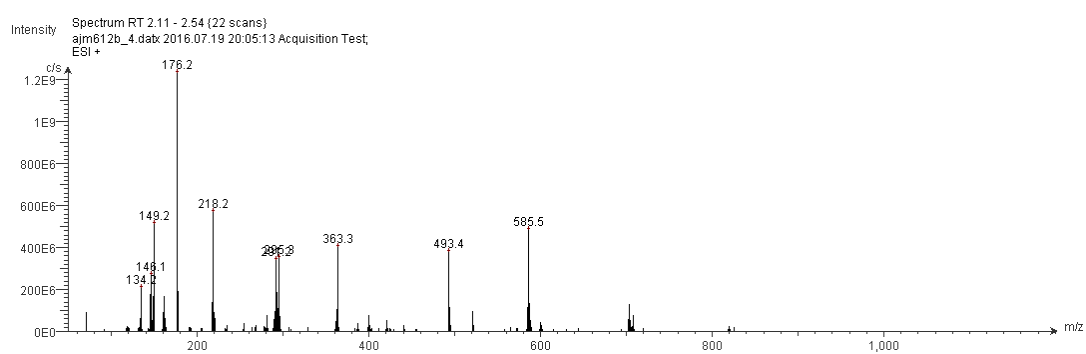
Aliquot, *ca.* 5 minutes after HBcat addition:



Aliquot, *ca.* 15 minutes after HBcat addition

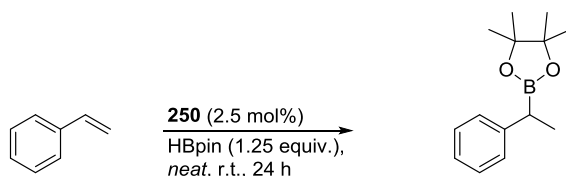


Aliquot, *ca.* 30 minutes after HBcat addition

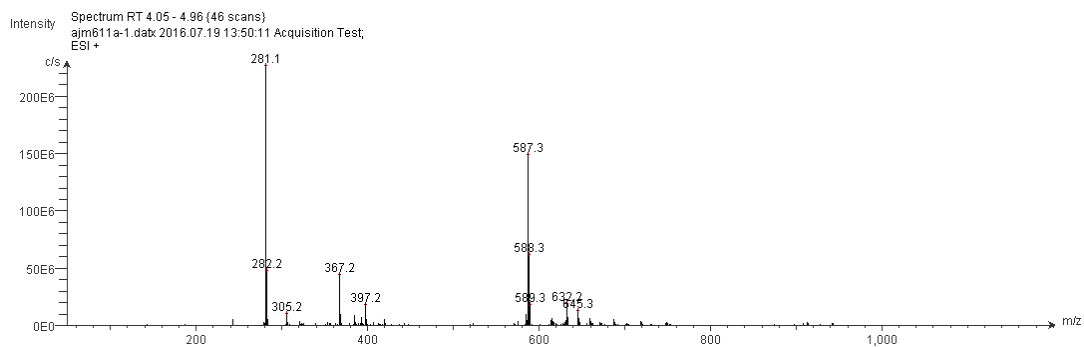


## Complex 250: Hydroboration of alkenes with pinacolborane

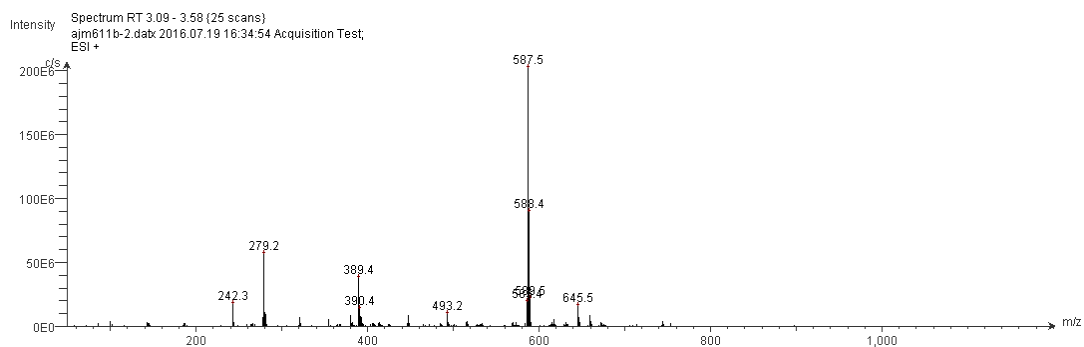
Pinacol borane (0.080 g, 0.091 mL, 0.63 mmol, 1.25 equivalents) was added to is[1-(mesityl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) **250** (0.031 g, 0.05 mmol, 0.025 equivalents) followed 15 s later by a styrene derivate (0.50 mmol, 1 equivalent). Aliquots (*ca.* 5  $\mu$ L) were removed from the reaction mixture and analysed by ESI-MS.



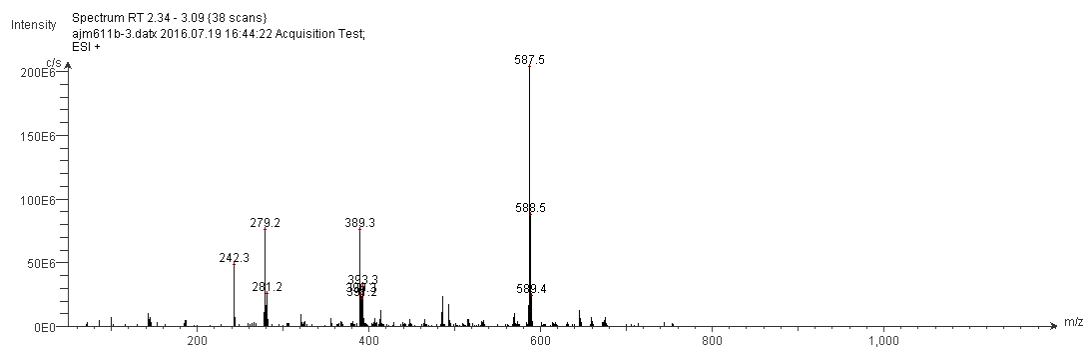
Aliquot, immediately after alkene addition:



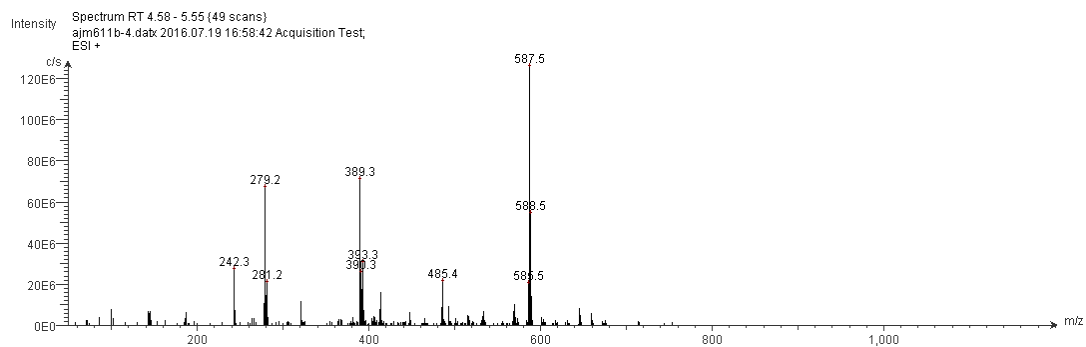
Aliquot, *ca.* 5 minutes after alkene addition:



Aliquot, *ca.* 15 minutes after alkene addition



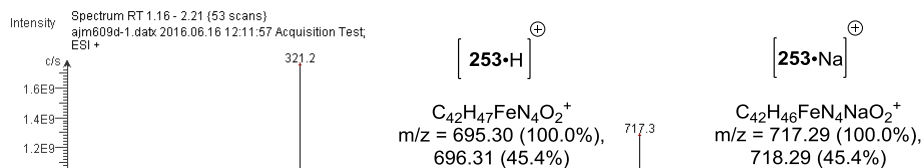
Aliquot, *ca.* 30 minutes after alkene addition



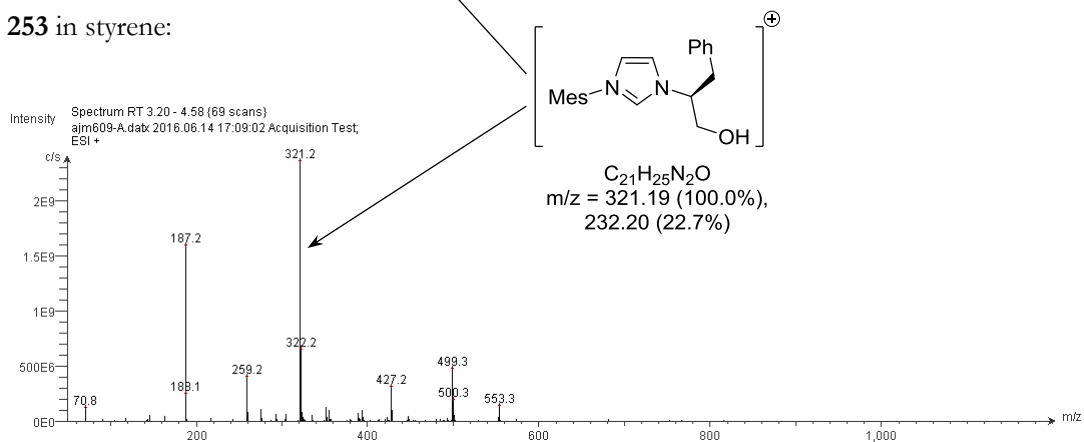


## Complex 253

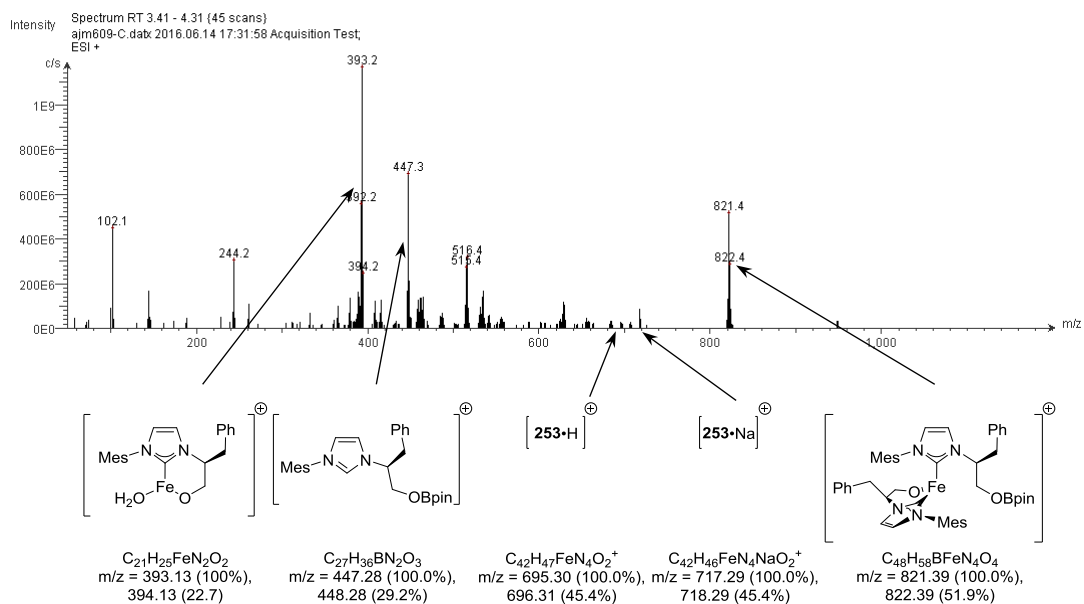
253 in tetrahydrofuran:



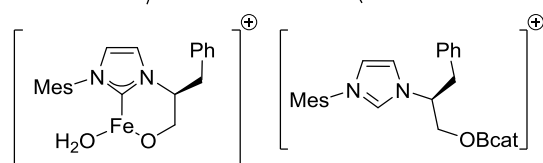
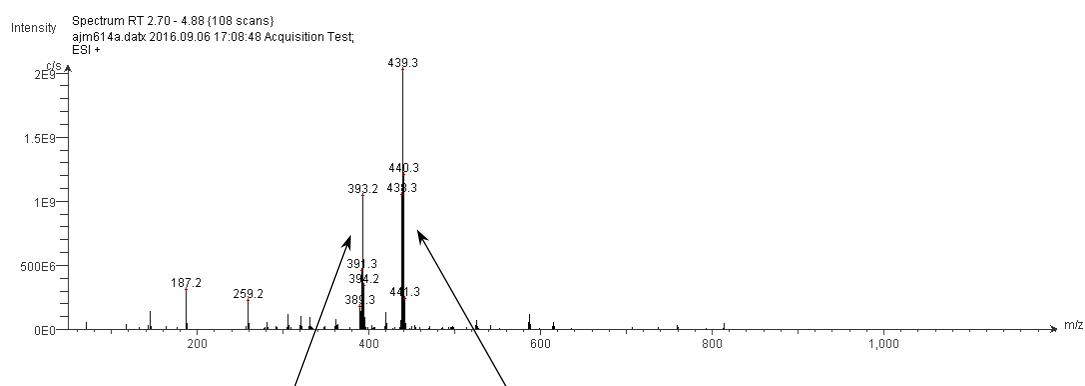
253 in styrene:



253 in HBpin:



## 253 in HBcat:

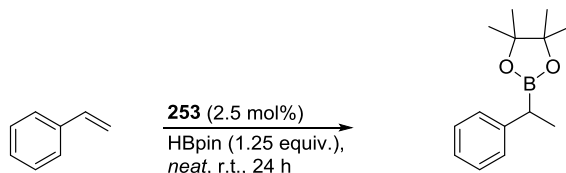


$\text{C}_{21}\text{H}_{25}\text{FeN}_2\text{O}_2^+$   
m/z = 393.13 (100%),  
394.13 (22.7)

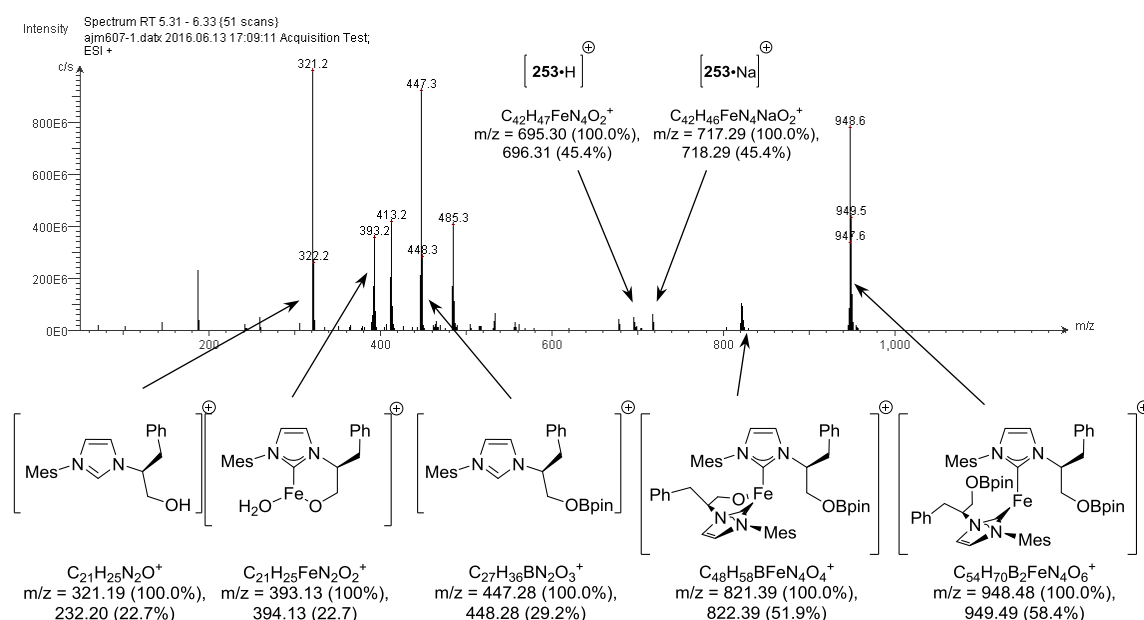
$\text{C}_{27}\text{H}_{28}\text{BN}_2\text{O}_3^+$   
m/z = 439.22 (100.0%),  
438.22 (24.8%)

## Complex 253: Hydroboration of alkenes with pinacolborane

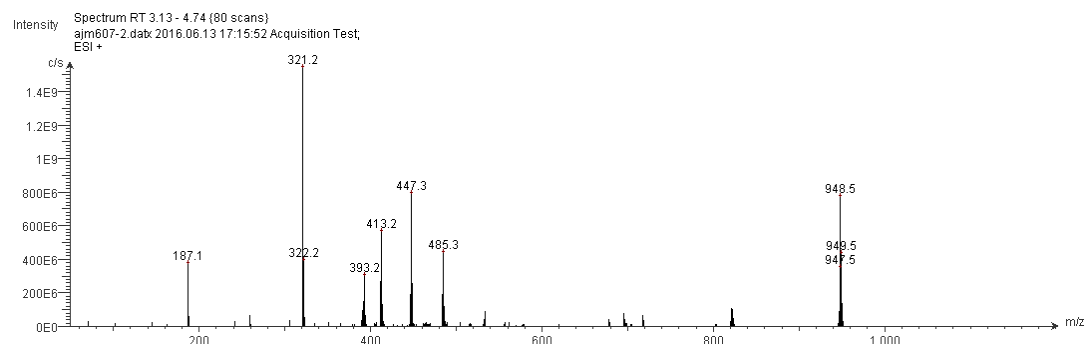
Pinacol borane (0.080 g, 0.091 mL, 0.63 mmol, 1.25 equivalents) was added to bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol, 0.025 equivalents), followed 15 s later by a styrene derivate (0.50 mmol, 1 equivalent). The resulting mixture was stirred at room temperature for 4 h. Aliquots (*ca.* 5  $\mu$ L) were removed from the reaction mixture and analysed by ESI-MS.

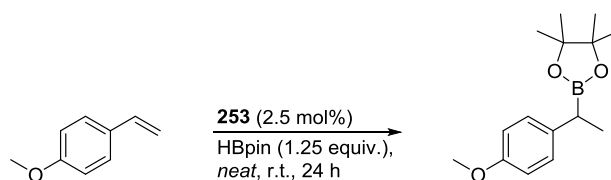


Aliquot, *ca.* 5 minutes after alkene addition:

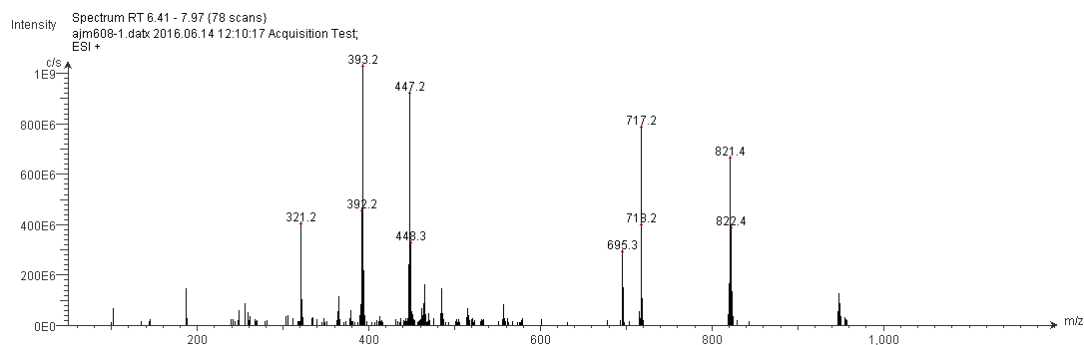


Aliquot, *ca.* 15 minutes after alkene addition

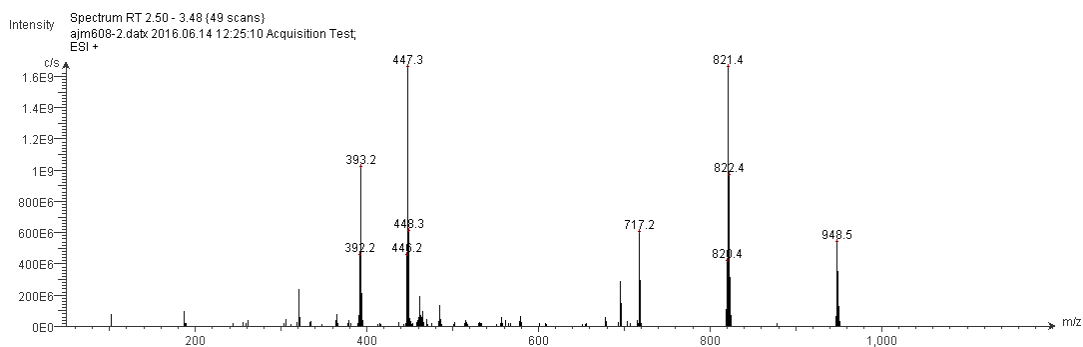




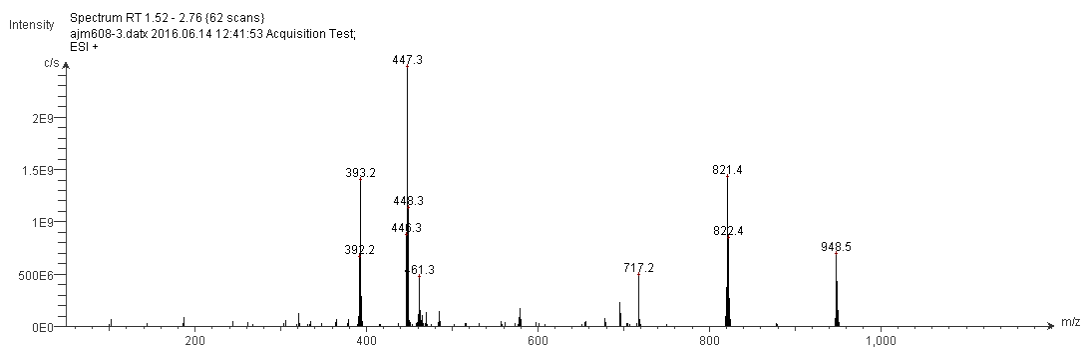
Aliquot, *ca.* 5 minutes after alkene addition



Aliquot, *ca.* 15 minutes after alkene addition

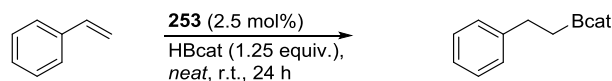


Aliquot, *ca.* 30 minutes after alkene addition

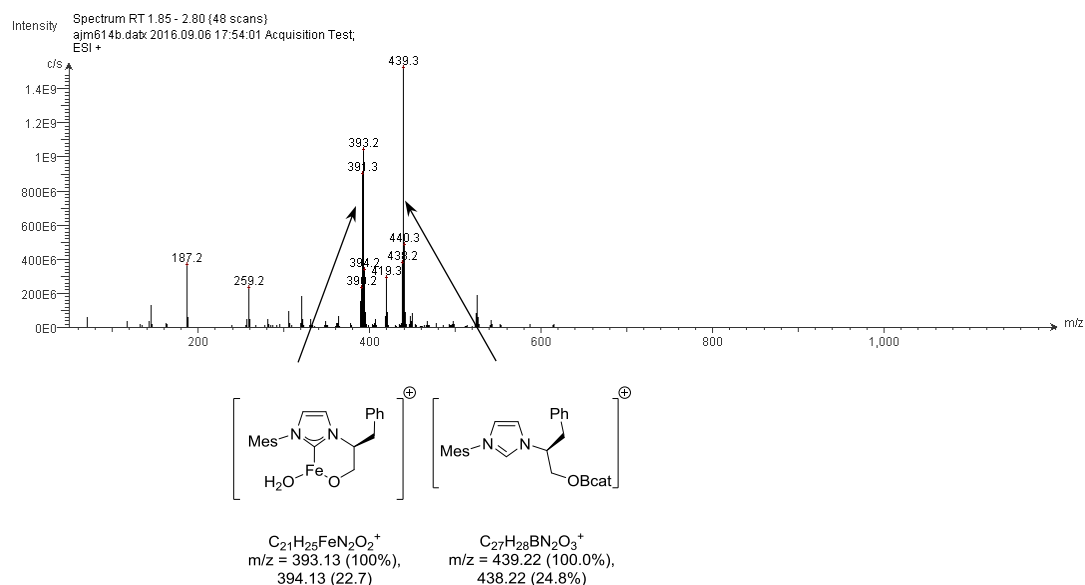


## Complex 253: Hydroboration of alkenes with catecholborane

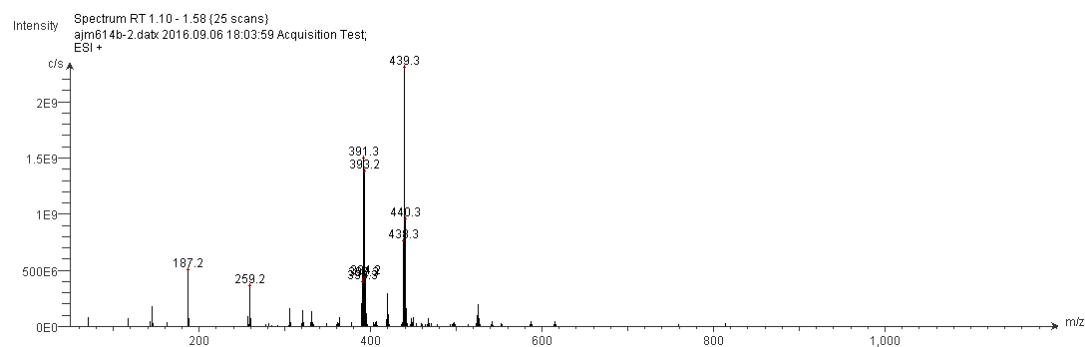
Catecholborane (0.075 g, 0.066 mL, 0.63 mmol, 1.25 equivalents) was added to bis{1-[mesityl]-3-[(*S*)-2*N*-3-phenylpropanoxy]-4,5-dihydro-imidazolyl} iron(II) **253** (0.009 g, 0.01 mmol, 0.025 equivalents), followed 15 s later by a styrene derivate (0.50 mmol, 1 equivalent). The resulting mixture was stirred at room temperature for 4 h. Aliquots (*ca.* 5  $\mu$ L) were removed from the reaction mixture and analysed by ESI-MS.



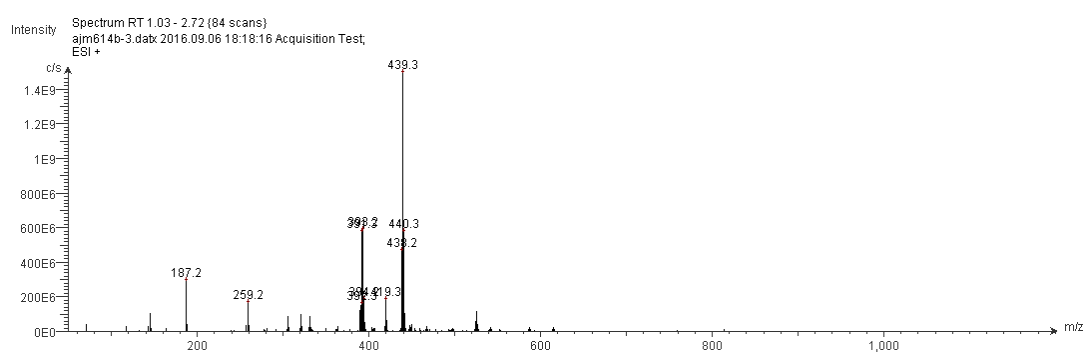
Aliquot, *ca.* 5 minutes after alkene addition



Aliquot, *ca.* 15 minutes after alkene addition



Aliquot, *ca.* 30 minutes after alkene addition



## 5.18 X-RAY CRYSTALLOGRAPHY DATA (SUMMARY)

Compound Identifier	Complex 250 se4002	Complex 251 se4003	Complex 252 se4004	Complex 253 se16004
Formula	C <sub>40</sub> H <sub>46</sub> FeN <sub>4</sub> O <sub>3</sub>	C <sub>42</sub> H <sub>50</sub> FeN <sub>4</sub> O <sub>5</sub>	C <sub>36</sub> H <sub>36</sub> N <sub>6</sub> O <sub>6</sub> Fe	C <sub>150</sub> H <sub>162</sub> F <sub>12</sub> Fe <sub>4</sub> N <sub>12</sub> O <sub>6</sub> P <sub>2</sub>
$D_{calc}/\text{g cm}^{-3}$	1.296	1.303	1.428	1.306
$\mu/\text{mm}^{-1}$		3.576	4.164	0.506
Formula Weight	686.66	746.71	704.56	2742.25
Colour	dark green	yellow	red	brown
Shape	block	block	cylinder	block
Max Size/mm	0.58	0.15	0.14	0.68
Mid Size/mm	0.24	0.12	0.04	0.30
Min Size/mm	0.06	0.05	0.03	0.13
T/K	120.0	120.0	120.0	120.0
Radiation Type		CuK $\alpha$	CuK $\alpha$	MoK $\alpha$
Crystal System	orthorhombic	monoclinic	monoclinic	orthorhombic
Flack Parameter				-0.0143(15)
Hooft Parameter				-0.0113(13)
Space Group	P b c n	P2 <sub>1</sub>	P2 <sub>1</sub> /n	P2 <sub>1</sub> 2 <sub>1</sub> 2
$a/\text{\AA}$	24.0256(5)	15.49431(14)	8.0949(2)	22.7811(6)
$b/\text{\AA}$	13.1262(3)	16.23501(13)	23.7481(5)	22.9453(6)
$c/\text{\AA}$	22.3213(6)	15.84297(16)	17.1961(5)	13.3383(3)
$\alpha/^\circ$	90	90	90	90
$\beta/^\circ$	90	107.2868(10)	97.427(3)	90
$\gamma/^\circ$	90	90	90	90
$V/\text{\AA}^3$	7039.4(3)	3805.28(6)	3278.00(15)	6972.2(3)
Z	8	4	4	2
Z'		2	1	0.5
$\Theta_{min}/^\circ$	2.935	2.987	3.191	2.507
$\Theta_{max}/^\circ$	31.177	76.311	76.258	28.315
Measured Refl.	145241	62592	50139	321877
Independent Refl.	10975	15668	6812	17128
Reflections Used		14557	5437	16121
$R_{int}$	0.0553	0.0438	0.0772	0.0349
Parameters	439	953	449	847
Restraints	0	1	0	12
Largest Peak	0.408	0.465	0.252	0.442
Deepest Hole	-0.430	-0.280	-0.377	-0.296
GooF	1.080	1.026	1.034	1.083
$wR_2$ (all data)	0.1099	0.0803	0.1000	0.0770
$wR_2$	0.1030	0.0783	0.0933	0.0739
$R_1$ (all data)	0.0631	0.0367	0.0635	0.0323
$R_1$	0.0460	0.0323	0.0462	0.0282
CCDC number	1487368	1487369	1487370	1487371

## REFERENCES

- (1) de Vries, J. G.; Jackson, S. D. *Catal. Sci. Technol.* **2012**, 2 (10), 2009–2009.
- (2) Smil, V. *Nature* **1999**, 400 (6743), 415–415.
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## APPENDIX 1: PUBLICATIONS

1. Iron-catalysed, general and operationally simple formal hydrogenation using  $\text{Fe}(\text{OTf})_3$  and  $\text{NaBH}_4$ . MacNair, A. J.; Tran, M.-M.; Nelson, J. E.; Sloan, G. U.; Ironmonger, A.; Thomas, S. P. *Org. Biomol. Chem.* **2014**, 12 (28), 5082-5088.
2. Markovnikov-Selective, Activator-Free Iron-Catalyzed Vinylarene Hydroboration. MacNair, A. J.; Millet, C. R. P.; Nichol, G. S.; Ironmonger, A.; Thomas, S. P. *ACS Catal.*, 2016, 6 (10), 7217-7221.

## **APPENDIX 2: NMR SPECTRA**

Please find copies of NMR spectra on attached CD.

## **APPENDIX 3: X-RAY CRYSTALLOGRAPHIC DATA**

Please find X-ray crystallographic reports, CIF files and Checkcif reports on attached CD.

### Iron-catalysed, general and operationally simple formal hydrogenation using $\text{Fe}(\text{OTf})_3$ and $\text{NaBH}_4$ †‡

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An operationally simple and environmentally benign formal hydrogenation protocol has been developed using highly abundant iron (iii) salts and an inexpensive, bench stable, stoichiometric reductant,  $\text{NaBH}_4$ , in ethanol, under ambient conditions. This reaction has been applied to the reduction of terminal alkenes (22 examples, up to 95% yield) and nitro-groups (26 examples, up to 95% yield). Deuterium labelling studies indicate that this reaction proceeds *via* an ionic rather than radical mechanism.

## Introduction

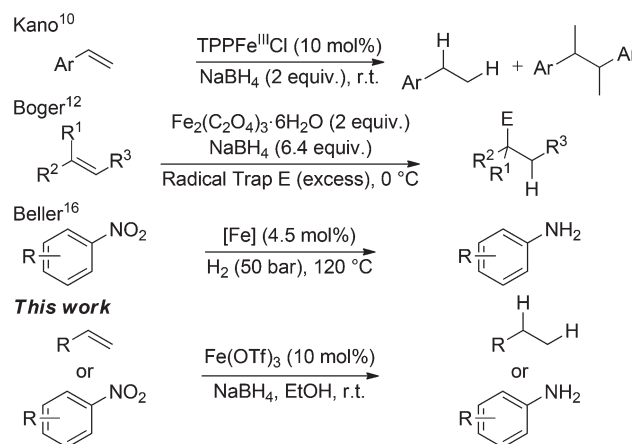
The hydrogenation of apolar and polar functionalities is routine in both academia and industry for the production of fine and bulk chemicals.<sup>1</sup> Highly operationally simple hydrogenation methods using heterogeneous (*e.g.*  $\text{Pd/C-H}_2$ ) or homogeneous (*e.g.*  $\text{Ru}/\text{NET}_3\text{-HCO}_2\text{H}$ ) systems have allowed the broadest possible user base to exploit this reaction.<sup>2</sup> To date, the most commonly used methods require precious or semi-precious transition metal complexes or finely divided powders.<sup>1</sup>

Iron-based catalysts offer several advantages over more traditional 'noble' metal systems due to the high abundance, long-term availability,<sup>3</sup> low cost and low toxicity of iron.<sup>4</sup> On an industrial scale, heterogeneous iron catalysts have been widely exploited; however the use of soluble iron catalysts is considerably less well developed.<sup>5</sup>

Iron-catalysed alkene reductions have been reported however many systems suffer from the need for: elevated temperatures; high hydrogen pressure; chemical activation or are superstoichiometric in iron.<sup>6</sup> Although several well defined

and highly active homogeneous iron complexes for catalytic hydrogenation have been developed,<sup>7</sup> notably by Chirik,<sup>8</sup> these catalysts and pre-catalysts are highly air- and moisture-sensitive, so have not seen widespread adoption. On a small scale, the use of hydrogen gas has numerous drawbacks, particularly with safe storage and handling. These can be circumvented by the use of an inexpensive, bench-stable, solid hydrogen source.  $\text{NaBH}_4$  is air- and moisture stable and produced on kilotonne scale annually.<sup>9</sup>

Ashby used  $\text{LiAlH}_4$  in conjunction with stoichiometric amounts of transition metal halides, including  $\text{FeCl}_3$  and  $\text{FeCl}_2$ , to reduce 1-octene.<sup>10</sup> Kano reported a biomimetic reduction of styrene derivatives using an iron-porphinato complex and  $\text{NaBH}_4$  however reductive homocoupling of radical species was a major side-reaction.<sup>11</sup> Recently, Boger reported the hydrofunctionalisation of alkenes mediated by superstoichiometric iron(III) salts and  $\text{NaBH}_4$ .<sup>12</sup> In the absence of an electrophile, it was found that tertiary alkenes were hydrogenated (Scheme 1).<sup>12a</sup>



**Scheme 1** Iron-catalysed reductions and reductive functionalisations. TTP = tetraphenylporphyrinato. [Fe] = iron phenanthroline complex pyrolysed onto a carbon support.

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†We dedicated this paper to Dr Stuart Warren on the occasion of his 75th birthday.

‡Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00945b





Along with alkene hydrogenation, the reduction of nitroarenes to aniline derivatives represent another high-value industrial process for the preparation of a wide range of synthetic precursors, including; dyes, pharmaceuticals, agrochemicals and polymers.<sup>13</sup> Iron-catalysed hydrogenation of nitroarenes is well established using iron(0) carbonyl precursors acting *via* a cohort of *in situ* generated iron species.<sup>14</sup> Beller has developed a number of homogeneous iron-catalysed nitroarene reductions<sup>15</sup> and recently carbon-supported heterogeneous systems using either  $\text{N}_2\text{H}_4 \cdot 6\text{H}_2\text{O}$  or  $\text{H}_2$  as the stoichiometric reductant (Scheme 1).<sup>16</sup>

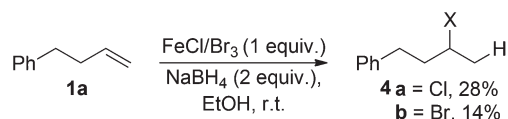
$\text{NaBH}_4$  is a poor reducing agent for nitro-groups under ambient conditions, although it has been used in the presence of palladium, nickel, copper catalysts for the reduction of nitro-groups to amines.<sup>17</sup> Additionally, Sakaki and co-workers have reported the use of  $\text{NaBH}_4$  and porphyrinatoiron complexes for the reduction of a limited number of nitroarenes.<sup>18</sup>

Herein we report an iron-catalysed,  $\text{NaBH}_4$ -mediated reduction procedure that is capable of reducing both alkene and nitroarene functionalities.

## Results and discussion

Alkene reduction was first investigated and successful 'hydrogenation' of 4-phenyl-1-butene **1a**, to the alkane **2a**, was found using stoichiometric (Table 1, entries 1–4) and substoichiometric (entries 5–10) amounts of simple, commercially available, iron salts in the presence of  $\text{NaBH}_4$ .<sup>19</sup>

Iron(III) chloride, bromide and triflate supported the reduction (entries 1–4); however when stoichiometric  $\text{FeCl}_3$  or



Scheme 2 Formation of halogenated side products, X = Cl/Br.

$\text{FeBr}_3$  were used, (3-chlorobutyl)benzene **4a** and (3-bromobutyl)benzene **4b** were obtained as side-products respectively. This was presumably as a result of radical formation, followed by halide abstraction from the iron salt (Scheme 2).<sup>20</sup>

Use of  $\text{Fe}(\text{OTf})_3$  prevented the halogenation reaction and in addition, it was found that  $\text{Fe}(\text{OTf})_3$  gave the shortest reaction times.<sup>21</sup> At a 10 mol% iron loading, the quantity of  $\text{NaBH}_4$  could be lowered to 1.5 equivalents and the reaction time reduced to 6 hours, without decreasing reaction yield (entry 8), however in all cases, it was found the some isomerisation to the internal alkene **3** was observed. An attempt to reduce the catalyst loading to 1 mol% gave considerably diminished yields, even after 48 h (entry 9).

The catalytic activity of iron was attested to by high purity  $\text{FeCl}_3$  (>99.99%) showing equal catalytic activity (entry 6) to the reagent grade salts.<sup>22</sup> Additionally in the absence of iron, no reduction of the alkene was observed: triflic acid and sodium triflate (entries 11 and 12) were not catalytically active; only the starting material **1a** was recovered.

Presumably due to the high solubility of  $\text{NaBH}_4$  in these solvents, successful reduction reactions were achieved in methanol, 1-butanol, 2-butanol and acetonitrile, however the highest yields were obtained in ethanol.<sup>19</sup> Along with the sustainability and low toxicity of ethanol, makes it the favoured reaction solvent.

With the optimal conditions of  $\text{Fe}(\text{OTf})_3$  (10 mol%),  $\text{NaBH}_4$  (150 mol%) in ethanol, the substrate scope of the formal hydrogenation was investigated. The developed system was found to be chemoselective for the reduction of terminal alkenes (Table 2). Reductions in the presence of aryl halides showed no protodehalogenation<sup>23</sup> except in the case of aryl bromide **1d** where 18% of the protodehalogenated product was observed (Table 2, entries 2–4).

Despite previous reports of the reduction of esters and amides with  $\text{NaBH}_4$  in  $\text{MeOH}$ ,<sup>24</sup> chemoselective alkene reduction was observed for substrates being both ester and amide functionalities (entries 6–8). Although a carboxylic acid functionalised substrate was poorly tolerated (entry 5), reduction of 4-phenyl-1-butene **1a** in the presence of acetic acid, using excess  $\text{NaBH}_4$ , was successful. Despite the lability of benzyl protecting groups under conventional hydrogenation conditions, both benzyl and silyl ethers were conserved during alkene reduction (entries 9 and 10).

Although the reduction was carried out in ethanol, inclusion of an alcohol or ketone in the alkene substrate diminished reduction yields (entries 12 and 13). Styrene derivatives were successfully reduced; however longer reaction times and higher quantities of  $\text{NaBH}_4$  were required and yields were generally lower than the alkyl analogues (entries 14–17).

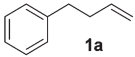
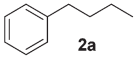
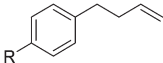
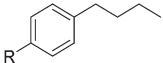
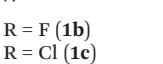
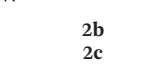
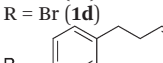
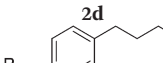
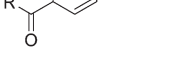
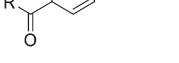
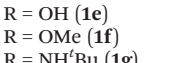
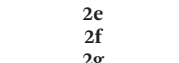
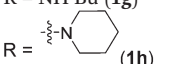
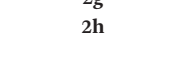
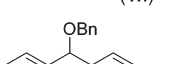
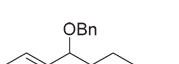
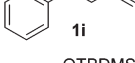
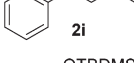
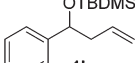
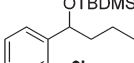
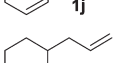
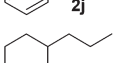
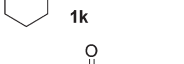
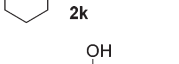
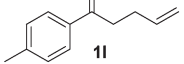
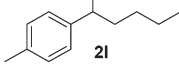
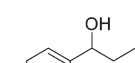
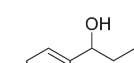
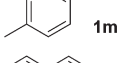
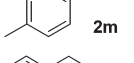
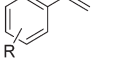
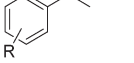
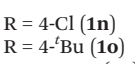
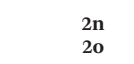
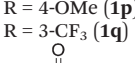
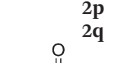
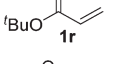
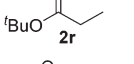
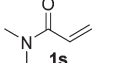
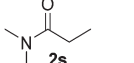
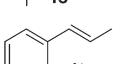
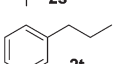
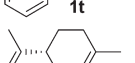
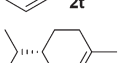
Table 1 Initial screen of activity of iron salts for the reduction of 4-phenyl-1-butene<sup>a</sup>

Entry	$\text{FeX}_{2/3}$	$\text{FeX}_{2/3}$ (mol%)	Equiv. $\text{NaBH}_4$	Yield <sup>b</sup> (%)	
				2a	3
1	$\text{FeCl}_3$	100	2	15	2
2	$\text{FeBr}_3$	100	2	42	1
3	$\text{Fe}(\text{OTf})_3$	100	1	19	3
4	$\text{Fe}(\text{OTf})_3$	100	2	91	9
5	$\text{FeCl}_3$	10	2	91	5
6	$\text{FeCl}_3^c$	10	2	89	6
7	$\text{Fe}(\text{OTf})_3$	10	2	90	10
8	$\text{Fe}(\text{OTf})_3^d$	10	1.5	90	10
9	$\text{Fe}(\text{OTf})_3^e$	1	2	47	7
10	$\text{Fe}(\text{OTf})_2$	10	2	11	0
11	$\text{HOTf}$	10	2	6	0 <sup>f</sup>
12	$\text{NaOTf}$	10	2	4	0 <sup>g</sup>

<sup>a</sup> Conditions: 0.50 mmol 4-phenyl-1-butene, *n* mol% iron(III) salt, *n* equiv.  $\text{NaBH}_4$ , EtOH (2 ml), r.t., 16 h. <sup>b</sup> Yield measured by <sup>1</sup>H NMR of the crude reaction product using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> >99.99% purity. <sup>d</sup> 6 h. <sup>e</sup> 48 h. <sup>f</sup> 75% starting material recovered. <sup>g</sup> 80% starting material recovered.



Table 2 Scope and limitation of the iron-catalysed, hydride-mediated reduction<sup>a</sup>

$  \begin{array}{ccc}  \text{R} \text{---} \text{CH}=\text{CH}_2 & \xrightarrow[\text{NaBH}_4, \text{EtOH}]{\text{Fe(OTf)}_3 (10 \text{ mol\%})} & \text{R} \text{---} \text{CH}_2\text{CH}_2\text{H} \\  \text{1a-v} & & \text{2a-v} \\  & & \text{r.t., 6 h}  \end{array}  $			
Entry	Substrate	Product	Yield <sup>b</sup> (%)
1			90 (83)
2			92 (79)
3			93 (77)
4			78 (71) <sup>c</sup>
5			25
6			95 (94)
7			73
8			92 (87)
9			50 (50)
10			56
11			>95 (69)
12			22
13			10
14			58 <sup>d</sup>
15			55 (45) <sup>d</sup>
16			56 (46) <sup>d</sup>
17			50 <sup>d</sup>
18			>95 (73)
19			75
20			3
21			0
22			7, 34 <sup>e</sup>

<sup>a</sup> Conditions: 1 mmol alkene, 10 mol% Fe(OTf)<sub>3</sub>, EtOH (4 ml), 1.5 equiv. NaBH<sub>4</sub>, r.t., 6 h. <sup>b</sup> Determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses. <sup>c</sup> 18% phenylbutane **2a** also recovered. <sup>d</sup> Conditions: 1 mmol alkene, 10 mol% Fe(OTf)<sub>3</sub>, EtOH (4 ml), 2 equiv. NaBH<sub>4</sub>, r.t., 18 h. <sup>e</sup> 20 equiv. NaBH<sub>4</sub>.



In contrast to the work of de Vries using iron nanoparticles,<sup>25</sup> acrylate and acrylamide derivatives were chemoselectively reduced at the alkene (entries 18 and 19). The reaction was highly selective for the reduction of unsubstituted terminal alkenes; only trace reduction of  $\beta$ -methyl styrene **1t** was observed and neither the internal nor 1,1-disubstituted alkenes of (+)-limonene **1u** underwent reduction (entries 20 and 21).<sup>26</sup> Attempts to extend the reaction scope to the terminal alkyne; 5-phenyl-butyne **1v**, resulted in a poor yield of alkane, even with excess NaBH<sub>4</sub> (entry 22). The reduction of 4-phenyl-1-butene in the presence of 10 mol% diphenylacetylene resulted in a reduced yield of phenylbutane (15%) and no evidence of reduction of the diphenylacetylene.

During the development of the alkene 'hydrogenation', the reduction of the nitro-group of 3-nitrostyrene was observed to occur competitively with the reduction of the alkene. Using nitrobenzene as a model substrate, simple iron salts were investigated for catalytic activity in the reduction of the nitro-group to primary amines. FeCl<sub>3</sub> offers an inexpensive and readily available iron(III) source and good reactivity was found with increased NaBH<sub>4</sub> loading (Table 3, entries 1–3). The use of high-purity FeCl<sub>3</sub> ( $\geq 99.99\%$ ) again did not change the observed reactivity, (entry 4). However, returning to Fe(OTf)<sub>3</sub> gave higher conversions to aniline (entry 6), and allowed reaction times to be reduced to 4 h.

Even using the apparently more active salt, Fe(OTf)<sub>3</sub>, it was found that the quantity of NaBH<sub>4</sub> could not be reduced without diminishing conversion to the product. In the absence of an iron salt, no reduction of nitrobenzene to aniline was observed, irrespective of the amount of NaBH<sub>4</sub> used. Lewis acids; BF<sub>3</sub> and AlCl<sub>3</sub>, were ineffective as catalysts (entries 10 and 11) and the use of triflic acid (entry 12) also resulted in only starting material being recovered.

Using these conditions, substrate scope was investigated. *o*-, *m*-, *p*-Methyl nitrobenzene, and even the sterically hindered 2,6-dimethyl nitrobenzene were all successfully reduced (Table 4, entries 2–5). Nitroarenes bearing electron-withdrawing (–CF<sub>3</sub>) and electron-donating (–OMe) substituents were both tolerated (entries 6–10). Nitro-groups were successfully reduced in the presence of aryl-chloride and fluoride substituents without protodehalogenation (entries 11–14), however, 4-bromo-nitrobenzene **5o** was reduced to both 4-bromoaniline and to the proto-dehalogenated product aniline (entry 15).

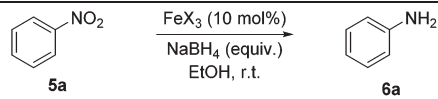
Chemoselective nitro-group reduction was observed in the presence of ester and amide functionalities (entries 17–19). The synthesis of the analgesic benzocaine **6r** from the corresponding nitroarene showcases the utility of this methodology. Perhaps unsurprisingly, a substrate bearing a ketone **5p** showed poor chemoselectivity with the carbonyl being reduced in addition to the nitro-group (entry 16).

*p*-(Methylthio)-aniline **5t** was successfully produced from the corresponding nitroarene in good yield (entry 20). The corresponding methylsulfonyl substituted nitroarene **5u** was also successfully reduced, albeit with lower isolated yield (entry 21). 8-Nitroquinoline **5w** was successfully reduced to 8-aminoquinoline (entry 23). Interestingly, treatment of nitro-substituted benzoxazole **5x** and benzothiazole **5y** derivatives with NaBH<sub>4</sub> in the absence of an iron salt exclusively gave the reductively ring-opened product. However, in the presence of Fe(OTf)<sub>3</sub>, only the chemoselective reduction of the nitro-group was observed (entries 24 and 25). Aliphatic nitro-groups were also reduced by the Fe(OTf)<sub>3</sub>/NaBH<sub>4</sub> system (entry 26), however increased loadings of both the catalyst and stoichiometric reductant were required.

Two contrasting mechanisms have been proposed for previously reported iron-catalysed, NaBH<sub>4</sub>-mediated, alkene reductions. We sought to gain insight into which of the following mechanisms is operating in our developed reaction conditions. Kano proposed the addition of an iron-hydride to the alkene, followed by proton abstraction from ethanol.<sup>11a</sup> In contrast, Boger proposed that both hydrogen atoms originated from sodium borohydride.<sup>12a</sup> Additionally, NaBH<sub>4</sub> has been shown to reduce iron(II/III) salts to a range of nanoparticulate or low oxidation-state iron and iron/boron species.<sup>25,27</sup> While the formation of nanoparticles cannot be ruled out, the lack of stabilisers or an induction period would appear to suggest against these being the active catalytic species. In order to investigate the origin of the added hydrogen, and gain insight into the mode of operation of the low-valent catalyst, a series of deuterium incorporation experiments were carried out.

Reduction of 4-phenyl-1-butene **1a** using NaBD<sub>4</sub> and d<sub>1</sub>-ethanol gave exclusively the dideuterated alkane d<sub>2</sub>-**2a** (Scheme 3a). In line with previous reports of deuterium exchange between NaBD<sub>4</sub> and alcoholic solvents,<sup>28</sup> performing the reduction with NaBD<sub>4</sub> and ethanol gave a mixture of deuterated and non-deuterated alkanes (Scheme 3b). In both cases deuterium was incorporated in both C3 and C4 positions of

Table 3 Optimisation of nitroarene reduction<sup>a</sup>

				
Entry	FeX <sub>2/3</sub>	NaBH <sub>4</sub> equiv.	<i>t</i> (h)	Conversion <sup>b</sup> (%)
1	FeCl <sub>3</sub>	2	18	15
2	FeCl <sub>3</sub>	4	18	51
3	FeCl <sub>3</sub>	20	18	88
4	FeCl <sub>3</sub> <sup>c</sup>	20	18	90
5	FeCl <sub>2</sub>	20	18	62
6	Fe(OTf) <sub>2</sub>	20	18	60
7	Fe(OTf) <sub>3</sub>	20	18	99
8	Fe(OTf) <sub>3</sub>	10	18	32
9	Fe(OTf) <sub>3</sub>	20	4	99
10	BF <sub>3</sub> ·Et <sub>2</sub> O	20	4	0 <sup>d</sup>
11	AlCl <sub>3</sub>	20	4	0 <sup>e</sup>
12	HOTf	20	4	1 <sup>f</sup>

<sup>a</sup> Conditions: 0.5 mmol 4-phenyl-1-butene, 10 mol% iron salt, NaBH<sub>4</sub>, ethanol (4 ml), r.t. <sup>b</sup> Conversion measured by <sup>1</sup>H NMR. <sup>c</sup> >99.99% purity. <sup>d</sup> 57% starting material recovered. <sup>e</sup> 31% starting material recovered. <sup>f</sup> 78% starting material recovered.



Table 4 Scope and limitation of the iron-catalysed, hydride-mediated reduction<sup>a</sup>

Entry	Substrate	Product	Yield <sup>b</sup> (%)	Entry	Substrate	Product	Yield <sup>b</sup> (%)
1	<b>5a</b>	<b>6a</b>	90 (80) <sup>c</sup>	14	<b>5n</b>	<b>6n</b>	80 (47)
2	<b>5b</b>	<b>6b</b>	80 <sup>d</sup> (80)	15	<b>5o</b>	<b>6o</b>	51 (51) <sup>e</sup>
3	<b>5c</b>	<b>6c</b>	61 <sup>d</sup> (49)	16	<b>5p</b>	<b>6p</b>	68 (15)
4	<b>5d</b>	<b>6d</b>	73 (66)	17	<b>5q</b>	<b>6q</b>	87 (80)
5	<b>5e</b>	<b>6e</b>	79 (59) <sup>c</sup>	18	<b>5r</b>	<b>6r</b>	93 (28)
6	<b>5f</b>	<b>6f</b>	76 <sup>d</sup> (75)	19	<b>5s</b>	<b>6s</b>	80 (32)
7	<b>5g</b>	<b>6g</b>	81 (68) <sup>c</sup>	20	<b>5t</b>	<b>6t</b>	>95 (76)
8	<b>5h</b>	<b>6h</b>	68 (24)	21	<b>5u</b>	<b>6u</b>	(53)
9	<b>5i</b>	<b>6i</b>	82 <sup>d</sup> (55)	22	<b>5v</b>	<b>6v</b>	82 (77) <sup>c</sup>
10	<b>5j</b>	<b>6j</b>	83 (76) <sup>c</sup>	23	<b>5w</b>	<b>6w</b>	54 (51)
11	<b>5k</b>	<b>6k</b>	73 <sup>d</sup>	24	<b>5x</b>	<b>6x</b>	33 (24)
12	<b>5l</b>	<b>6l</b>	87 <sup>d</sup>	25	<b>5y</b>	<b>6y</b>	60 (56)
13	<b>5m</b>	<b>6m</b>	70 <sup>d</sup> (17)	26	<b>5z</b>	<b>6z</b>	20 <sup>f</sup>

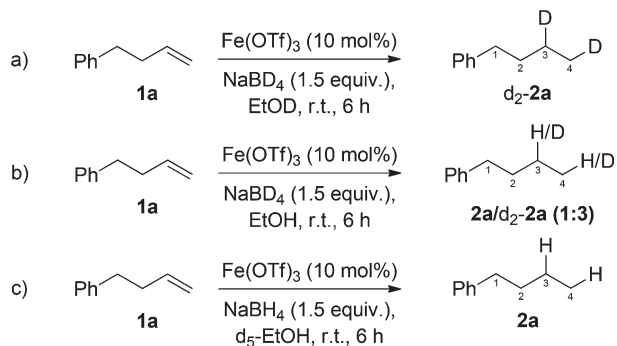
<sup>a</sup> Conditions: 0.5 mmol nitroarene, 10 mol% FeOTf<sub>3</sub>, EtOH (4 ml), 20 equiv. NaBH<sub>4</sub>, r.t., 4 h. <sup>b</sup> Yield determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses. <sup>c</sup> Isolated as the HCl salt. <sup>d</sup> 1,2-Dichloroethane used as internal standard. <sup>e</sup> 9% aniline also recovered. <sup>f</sup> Conditions: 50 mol% FeOTf<sub>3</sub>, 30 equiv. NaBH<sub>4</sub>.

the alkane. In order to probe the existence of a radical intermediate, d<sub>5</sub>-EtOH was used as the reaction solvent to probe radical abstraction from the CD<sub>2</sub>OH position, however, no deuterium incorporation was observed (Scheme 3c). This suggests an ionic, rather than radical mechanism.

## Conclusions

In conclusion, a single, general, operationally simple and highly applicable protocol for the formal hydrogenation of apolar (alkene) and polar (nitro-) functionalities has been deve-





**Scheme 3** Deuterium labelling studies for the investigation of the mechanism of iron-catalysed, NaBH<sub>4</sub> mediated, alkene reduction.

loped using a simple iron salt as catalyst. Using Fe(OTf)<sub>3</sub> (10 mol%) and NaBH<sub>4</sub> as the stoichiometric reductant, a wide range of functionalised and unfunctionalised alkenes and aryl- and alkyl nitro-groups have been successfully hydrogenated under operationally simple, environmentally benign reaction conditions.

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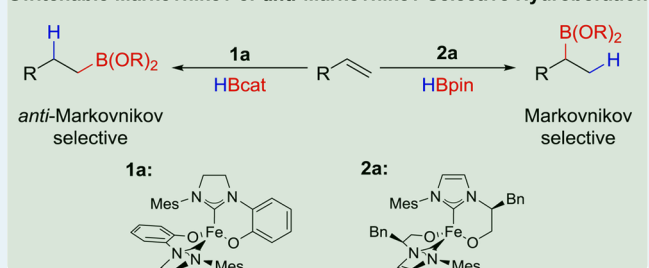
## Markovnikov-Selective, Activator-Free Iron-Catalyzed Vinylarene Hydroboration

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## Supporting Information

**ABSTRACT:** Two series of structurally related alkoxy-tethered NHC iron(II) complexes have been developed as catalysts for the regioselective hydroboration of alkenes. Significantly, Markovnikov-selective alkene hydroboration with HBpin has been controllably achieved using an iron catalyst (11 examples, 35–90% isolated yield) with up to 37:1 branched:linear selectivity. *anti*-Markovnikov-selective alkene hydroboration was also achieved using HBcat and modification of the ligand backbone (6 examples, 44–71% yields). In both cases, ligand design has enabled activator-free low-oxidation-state iron catalysis.

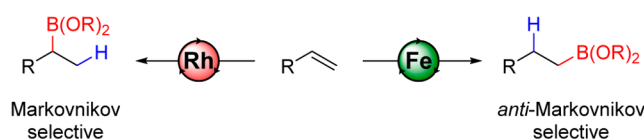
**KEYWORDS:** iron, catalysis, hydroboration, Markovnikov selectivity, NHC ligands

Switchable Markovnikov or *anti*-Markovnikov Selective Hydroboration

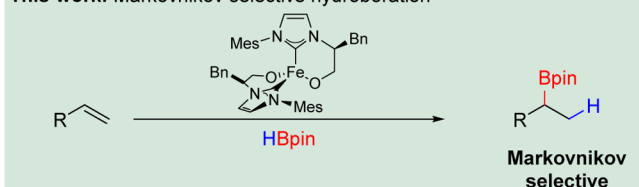
Boronic esters are ubiquitous in chemical synthesis due to the vast number of bond-forming reactions able to selectively transform these stable reagents into a wide-range of functionalities.<sup>1–4</sup> The hydroboration of alkenes using boranes is a well-established method for the synthesis of alkyl boranes, which can be converted to the bench-stable boronic esters in a straightforward manner.<sup>5,6</sup> In contrast, the hydroboration of alkenes using boronic esters leads directly to the alkyl boronic esters but requires the use of a precious metal catalyst, most commonly rhodium (Scheme 1).

## Scheme 1. Current State-of-the-Art in Metal-Catalyzed Alkene Hydroboration Reactions

## Established Reactivity:



## This work: Markovnikov selective hydroboration



Although high chemoselectivity, regioselectivity, and enantioselectivity can be achieved using precious metals,<sup>7–9</sup> there is still limited precedent for the direct generation of bench-stable pinacol boronic esters by use of pinacol borane (HBpin),<sup>10–12</sup> and precious metals suffer from inherent toxicity, cost, and sustainability concerns. To address these concerns, earth-abundant metal species have been developed as potential alternatives.<sup>13,14</sup>

A number of iron catalysts have been developed for the hydroboration using HBpin, or formal hydroboration using B<sub>2</sub>Pin<sub>2</sub> and an alkoxide, of alkene and alkynes to give the pinacol boronic esters directly (Scheme 1).<sup>15–24</sup> In all cases, these hydroboration reactions are either highly *anti*-Markovnikov-selective or give the Markovnikov product as a mixture with the *anti*-Markovnikov product. Recently reported by Webster and co-workers, the highest Markovnikov:*anti*-Markovnikov selectivity ranges from 60:40 to 70:30 for styrene derivatives.<sup>23</sup> Thus, there is a clear need for earth-abundant metal-catalyzed hydroboration reactions that proceeds with Markovnikov selectivity.<sup>25–27</sup>

To this end, we sought to develop a Markovnikov-selective iron-catalyzed hydroboration reaction. Ideally, this would be achieved using operationally simple conditions: easily handled reagents and without the need for an external activator. As part of our continuing research efforts on the development of novel

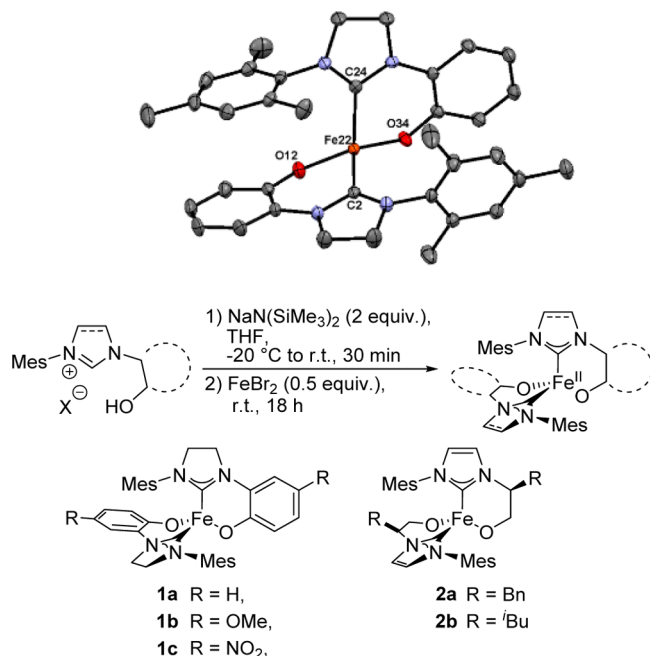
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activation modes for earth-abundant metal precatalysts, and given that alkoxy-tethered NHC ligands have been reported for the hydrosilylation of carbonyl derivatives,<sup>28,29</sup> we postulated that ligand assistance could be used to enable both precatalyst and boronic ester activation.

Three aryloxy-functionalized imidazolium salts were synthesized,<sup>30</sup> along with two alkoxy-functionalized imidazolium salts produced using a one-pot protocol.<sup>31</sup> These were deprotonated and reacted with FeBr<sub>2</sub> to give the five iron(II) complexes **1a–c** and **2a,b**, respectively (Scheme 2).<sup>32,33</sup> It is

**Scheme 2. Synthesis of Novel Fe(II) Complexes 1a–c and 2a,b; Molecular Structure of 1a<sup>a</sup>**



<sup>a</sup>Single-crystal X-ray analysis revealed that these bis-ligated complexes all adopted a similar distorted tetrahedral structure featuring an anchoring iron-carbene bond and the potentially activating group in the Fe–O motif (see Supporting Information (SI) for details). 50% probability ellipsoids; hydrogen atoms and solvent molecules omitted for clarity; Gray = C, Blue = N, Red = O, Orange = Fe. CCDC 1487368–1487371 contains the supplementary crystallographic data for complexes **1a–c** and **2a**.

worth noting at this point, that even with ligand synthesis, these iron catalysts were prepared in 2-steps and at considerably less cost than even commercially available Wilkinson's catalyst.<sup>34</sup>

Initial investigations into alkene hydroboration found success using catecholborane (HBcat). HBcat is known to perform alkene hydroboration at elevated temperatures, but the reaction proceeds only very slowly at room temperature (Table 1, entry 1).<sup>35,36</sup> In the presence of HBcat, complexes **1a–c** were shown to be catalytically active for the linear hydroboration of terminal alkenes in THF at room temperature (entry 2, see SI for further details). Using 5 mol % of aryloxy-tethered NHC-Fe<sup>II</sup> complex **1a**, the *anti*-Markovnikov hydroboration product **4** was obtained, following oxidation to give the linear alcohol **6a**,<sup>10</sup> in 81% yield. Interestingly, variation of the electronic character of the aryloxy-substituent on the catalyst led to diminished hydroboration yields (see SI for further details). Alkoxy-tethered NHC-Fe<sup>II</sup> complexes **2a,b** were considerably less

**Table 1. Reaction Optimization for the Hydroboration of Styrene Derivatives**

**rene derivatives<sup>a</sup>**

entry	[Fe] (mol %)	R	HBOR <sub>2</sub> (equiv)	yield (%) <sup>b</sup>	
				4	5
1 <sup>c</sup>	none	PhCH <sub>2</sub> CH <sub>2</sub>	HBcat (1.5)	25	-
2 <sup>c</sup>	<b>1a</b> (5.0)	PhCH <sub>2</sub> CH <sub>2</sub>	HBcat (1.5)	81	8
3 <sup>c</sup>	<b>2a</b> (5.0)	PhCH <sub>2</sub> CH <sub>2</sub>	HBcat (1.5)	30	-
4	<b>1a</b> (5.0)	PhCH <sub>2</sub> CH <sub>2</sub>	HBpin (2.0)	-	-
5	<b>1a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBpin (2.0)	-	6
6 <sup>d</sup>	<b>1a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBpin (2.0)	5	26 <sup>e</sup>
7 <sup>d</sup>	<b>2a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBpin (2.0)	3	25 <sup>e</sup>
8 <sup>d,f</sup>	<b>1a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBpin (1.0)	2	67 <sup>e</sup>
9 <sup>d</sup>	<b>2a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBpin (1.25)	8	70 <sup>e</sup>
10 <sup>d</sup>	<b>2a</b> (2.5)	4- <i>t</i> Bu-C <sub>6</sub> H <sub>4</sub>	HBcat (1.25)	37 <sup>e</sup>	-
11 <sup>d</sup>	<b>2a</b> (2.5)	PhCH <sub>2</sub> CH <sub>2</sub>	HBcat (1.25)	65 <sup>e</sup>	-

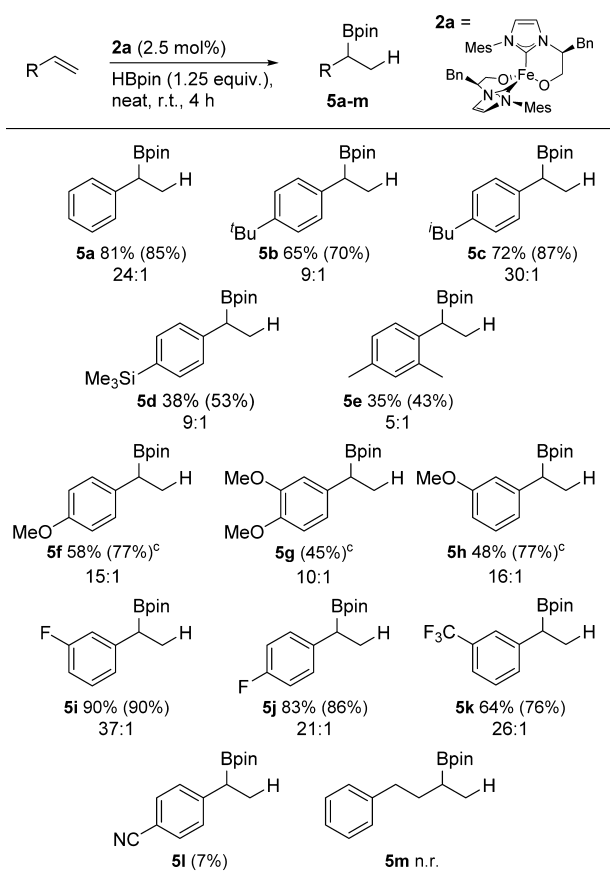
<sup>a</sup>Conditions: Boronic ester (equiv), [Fe] (2.5 to 5.0 mol %), and alkene (1 equiv) in THF (0.5 M), room temperature. <sup>b</sup>Yields determined by <sup>1</sup>H NMR relative to 1,3,5-trimethoxybenzene internal standard. <sup>c</sup>Isolated as the corresponding alcohols following oxidation with basic H<sub>2</sub>O<sub>2</sub>(aq). <sup>d</sup>Conditions: neat. <sup>e</sup>Conversions determined by integrals of benzylic product peaks in <sup>1</sup>H NMR relative to the limiting reagent. <sup>f</sup>4-*tert*-Butylstyrene (5 equiv).

active under these conditions (entry 3, see SI for further details).

Initial testing of aryloxy- and alkoxy-tethered NHC-Fe<sup>II</sup> complexes **1a–c** and **2a,b** for alkene hydroboration using pinacolborane (HBpin) resulted in alkene isomerization and hydrogenation only (Table 1, entries 4 and 5, for full details see SI). By performing the hydroboration of styrene derivatives with HBpin in the absence of solvent, mixtures of the secondary **5** and primary **4** alkylboronic ester products could be obtained (entries 6–9, see SI for further details). Significantly, the Markovnikov (branched) product was favored in all cases. Alkoxy-tethered NHC complex **2a** gave the best Markovnikov selectivity and yield of the secondary hydroboration product **5** (entry 7). Yields of the secondary boronic ester **5** could be increased for aryloxy-tethered NHC complex **1a**, but only by performing the reactions in an excess of the styrene derivative (entry 8). This was not necessary for alkoxy-tethered NHC complex **2a**, which gave synthetically useful isolated yields of the secondary boronic ester product using 1.25 equiv of HBpin (entry 9). Further variation of HBpin and catalyst loading gave no significant increase in yield (see SI for full details). Application of HBcat to the neat reaction conditions using alkoxy-tethered complex **2a**, led to formation of the linear hydroboration product (entries 10 and 11). These reaction mixtures were colorless and contained aggregates and the product mixtures were indistinguishable from uncatalyzed control reactions. This suggests that the alkoxy-tethered complex **2a** is decomposed by HBcat under these conditions, and that the background, *anti*-Markovnikov-selective reaction proceeds in this case.

The scope of the Markovnikov-selective hydroboration reaction was investigated using a range of electronically differentiated styrene derivatives, alkoxy-tethered NHC-Fe<sup>II</sup> **2a** (2.5 mol %), and HBpin (1.25 equiv) (Table 2). Styrene proved to be an excellent substrate giving the secondary

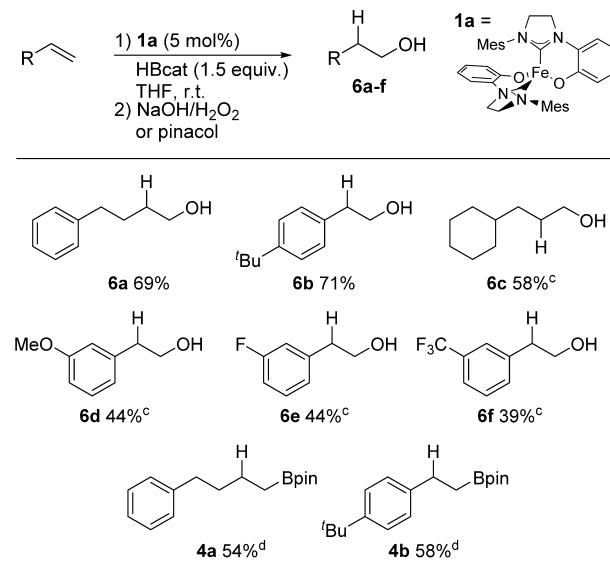


**Table 2. Iron-Catalyzed Markovnikov-Selective Hydroboration of Styrene Derivatives Using **2a**,**

<sup>a</sup>Conditions: HBpin (1.25 equiv) added in a single portion to **2a** (2.5 mol %), followed after ~15 s by alkene (1 equiv), room temperature, 4 h. <sup>b</sup>Isolated yields following flash column chromatography. Conversions in parentheses, and branched:linear ratios calculated from relative integrals of starting material and product peaks in <sup>1</sup>H NMR, average of at least 2 runs. <sup>c</sup>Product unstable on silica gel.<sup>37</sup>

boronic ester **5a** in 81% isolated yield, and a 24:1 branched:linear ratio, significantly increased regioselectivity compared to those previously reported.<sup>23</sup> Styrene derivatives bearing alkyl- and trialkylsilyl-substituents reacted in good yields (**5b–5d**, 38–72%) and branched:linear selectivities (9:1 to 30:1). Alkyl substituents could also be tolerated in the *ortho* position, with synthetically useful yields and branched:linear selectivities achieved (**5e**). Styrene derivatives bearing electron-donating aryl-substituents underwent successful hydroboration in moderate to good yields (35–72%) and selectivities (5:1 to 30:1) to give the branched boronic esters **5b–5g**. Styrene derivatives bearing electron-withdrawing aryl-substituents including fluoro- and trifluoromethyl groups gave the secondary alkyl-boronic esters **5h–5k** in good yields (48–90%) and excellent branched:linear ratios (16:1 to 37:1). Using 4-cyanostyrene resulted in only 7% of the alkene hydroboration product **5l**, along with a mixture of alkene and nitrile hydrogenation products. Alkyl-alkenes, such as 4-phenyl-1-butene, gave no conversion to the Markovnikov hydroboration product **5m** under these conditions with only starting material and a mixture of alkene isomerization products recovered from these reactions. Styrene derivatives bearing substituents at the  $\alpha$ - or  $\beta$ -position, such as  $\alpha$ -methylstyrene,  $\beta$ -methylstyrene, and indene, were all unreactive under the developed conditions.

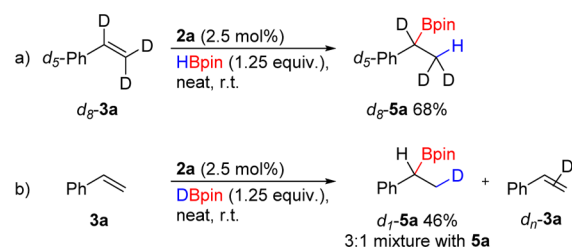
The substrate scope of the hydroboration to give primary alkylboronic esters was next investigated with aryloxy-tethered NHC catalyst **1a** (5 mol %), HBcat (1.5 equiv), and various alkenes (Table 3). Successful catalysis was achieved for terminal

**Table 3. Iron-Catalyzed *anti*-Markovnikov-Selective Hydroboration of Terminal Alkenes Using **1a**,**

<sup>a</sup>Conditions: HBcat (1.5 equiv) was added in a single portion to a solution of **1a** (5 mol %) and an alkene (1 equiv) in THF (0.5 M), room temperature, 5 h. Then an aqueous H<sub>2</sub>O<sub>2</sub>/NaOH solution was added in a single portion, 0 °C, 0.5 h. <sup>b</sup>Isolated yields following flash column chromatography. <sup>c</sup>Yield measured by <sup>1</sup>H NMR of crude reaction product relative to 1,3,5-trimethoxybenzene internal standard. <sup>d</sup>Instead of oxidation, pinacol (1 equiv) was added, room temperature, 18 h.

alkyl- and aryl- alkenes to give the primary alcohol products **6a–6f**, following oxidation with basic hydrogen peroxide. Alternatively, the catechol-boronic esters could be transesterified with pinacol to give the primary alkyl- boronic ester products **4a** and **4b**. Styrene derivatives bearing both electron-withdrawing and -donating arene substituents gave the primary alcohol products in roughly equal yields, albeit decreased from that obtained with alkyl-substituted alkenes.

In order to gain insight into the mechanism of the alkene hydroboration with HBpin, deuterium-labeling experiments were performed. Catalytic hydroboration of *d*<sub>5</sub>-styrene with HBpin gave the monoproton-boronic ester *d*<sub>5</sub>-**5a** exclusively with H incorporation at the terminal methyl group (Scheme 3a). When DBpin was used for the hydroboration of styrene

**Scheme 3. Deuterium-Labeling Studies of Markovnikov-Selective Alkene Hydroboration; Isolated Yields Following Flash Column Chromatography**

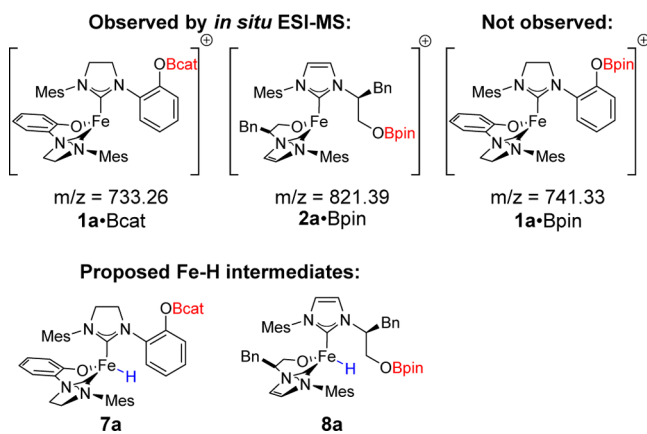
the monodeuterated boronic ester  $d_1$ -**5a** formed in a 3:1 mixture with the fully protio-boronic ester **5a** accompanied by deuterio-styrene  $d_n$ -**3a**, (Scheme 3b). This suggests that hydrometalation precedes C–B bond formation. In addition, the returned deuterio-styrene showed deuterium at both alkene carbons, suggesting  $\beta$ -hydride elimination occurs following hydrometalation, as an alternative to B–C bond formation. This  $\beta$ -hydride elimination accounts for the formation of fully protio-boronic ester observed when using DBpin.

Reaction monitoring by  $^{11}\text{B}$  NMR provided no evidence of any boron-containing species other than the product and HBpin in the reaction mixtures. Oxidation of the branched hydroboration product, followed by chiral HPLC analysis revealed no enantioenrichment of the secondary alcohol products, despite the enantioenriched ligand (see SI for details).

To further probe the mechanism, and given the lack of any enantioselectivity, the catalytic hydroboration of styrene with HBpin was performed in the presence of radical inhibitors TEMPO and galvinoxyl free radical. In both cases, increased loading of radical inhibitor was needed to considerably attenuate catalytic activity (see SI for details). The formation of neither alkyl-TEMPO nor alkyl-galvinoxyl adducts were observed. Diminished yields in the presence of free radical additives may simply be due to reactions between the additive and the iron catalyst.<sup>38,39</sup>

Having proposed that the alkoxy-tethered NHC ligands could act in conjunction with the  $\text{Fe}^{\text{II}}$  center to activate the boronic esters, investigation into the identity of the catalytic intermediates was paramount. ESI-MS was used to directly probe the reaction mixtures of both the *anti*-Markovnikov- and Markovnikov-selective hydroboration of styrene **3g** (Scheme 4).

**Scheme 4.** *In Situ* Reaction Monitoring by ESI-MS



Reactions of the *anti*-Markovnikov-selective catalyst **1a** with HBcat showed cleavage of the H–B bond to give an adduct bearing a borylated ligand (**1a·Bcat**  $m/z = 733.26$ ). The analogous reaction with HBpin led to no such borylation product being observed. However, when the Markovnikov-selective catalyst **2a** was used, HBpin was cleaved and borylated complexes **2a·Bpin** and **2a·(Bpin)<sub>2</sub>** ( $m/z = 821.39$  and  $948.48$ , respectively) were observed. The alkoxy-tethered complex **2a**, when treated with HBcat, gave only products of ligand dissociation and complex decomposition. This is in keeping with the results above, which indicated that **2a** is not a stable catalyst for hydroboration with HBcat.

Because the reaction conditions effectively catalyze the isomerization of terminal alkyl-substituted alkenes (*vide supra*), there is a strong implication that the reaction proceeds by alkene hydrometalation by an iron-hydride complex. The observed borylated iron complexes **1a·Bcat**, **2a·Bpin** (Scheme 4) are presumably derived from the corresponding iron-hydride complexes **7a** and **8a** respectively on ionization. We propose that the alkoxy-tethered ligand is more able to activate Bpin, promoting the formation of the required iron-hydride species and in contrast to the analogous reaction with HBcat, which only leads to decomposition of catalysts. The low activity of **1a** in the hydroboration of alkenes with HBpin is presumably due to the low reactivity of this ligand toward the activation of HBpin. It is not clear whether these reactions proceed by a single catalytic iron-hydride species or an ensemble thereof.

The regioselectivity of the Markovnikov-selective hydroboration of styrene derivatives with HBpin and alkoxy-tethered complex **2a** can be rationalized by the formation a stabilized benzyl-iron intermediate following hydrometalation. For the *anti*-Markovnikov-selective hydroboration reactions with the more electrophilic HBcat, where catalyst decomposition is observed, a Lewis acid/base-promoted,<sup>40</sup> or radical hydrogen-atom transfer<sup>41</sup> reactions cannot be ruled out. However, we also cannot exclude the formation of a kinetically favored terminal alkyl-iron intermediate when using HBcat. Further mechanistic investigations, in order to investigate the regioselectivity switch, and allow refinement of the catalyst design and expansion of the reaction scope, are still ongoing.

In summary, we have developed a series of novel  $\text{Fe}(\text{II})$  catalysts bearing alkoxy-tethered NHC ligands that are catalytically active for the hydroboration of terminal alkenes with controlled and switchable regioselectivity. Alkoxy-tethered NHC- $\text{Fe}^{\text{II}}$  complex **2a** is the first reported iron catalyst that is effective for the Markovnikov (branched)-selective hydroboration of styrene derivatives using HBpin. Additionally, aryloxy-tethered NHC- $\text{Fe}^{\text{II}}$  complex **1a** has been shown to be an effective catalyst for the *anti*-Markovnikov (linear)-selective hydroboration of terminal alkenes using HBcat. Mechanistic investigations suggest that ligand design facilitates a ligand-assisted catalyst activation. The proposed catalytically active hydride species enable iron-catalyzed hydroboration reactions to proceed in short reaction times at ambient temperatures and, most significantly, in the absence of any external activator.

## ■ ASSOCIATED CONTENT

### § Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02281.

Experimental procedures and compound characterization data (PDF)

Crystallographic data for compound **1a** (CIF)

Crystallographic data for compound **1b** (CIF)

Crystallographic data for compound **1c** (CIF)

Crystallographic data for compound **2a** (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ ACKNOWLEDGMENTS

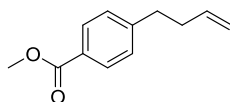
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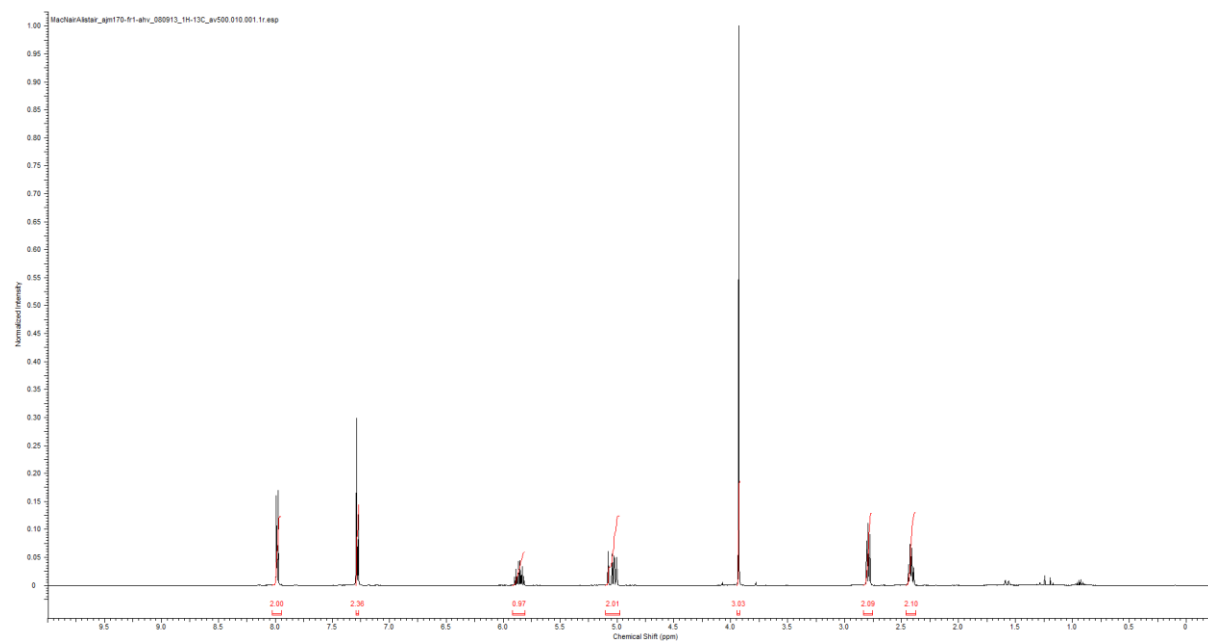
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# NMR Spectra

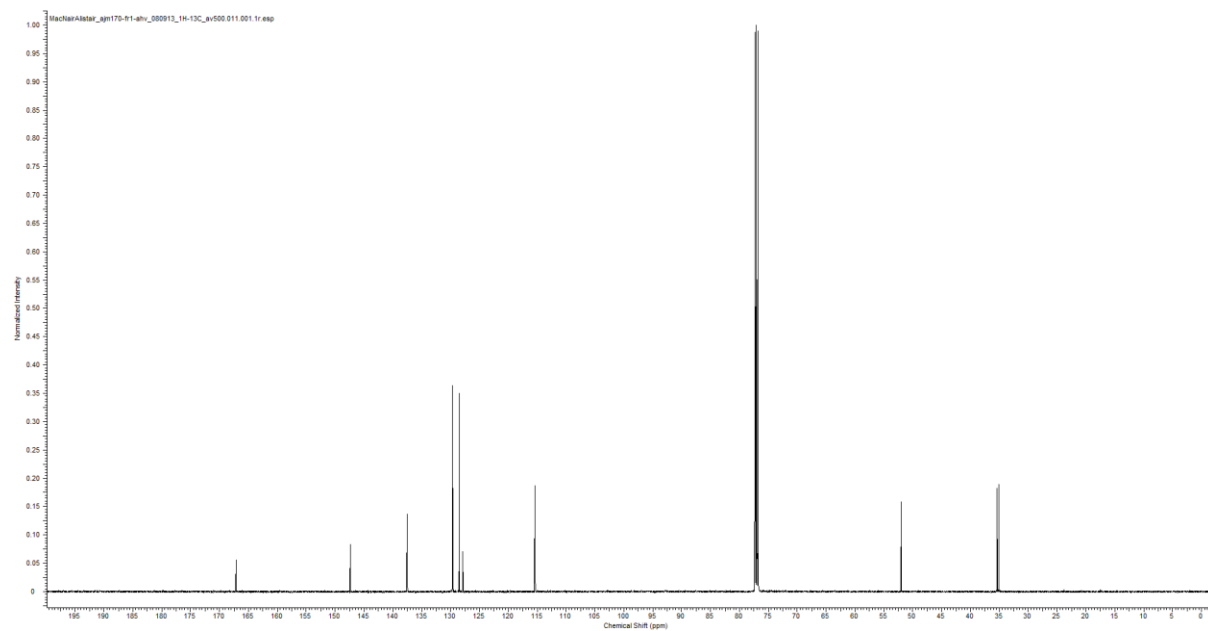
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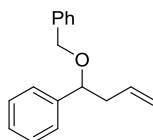
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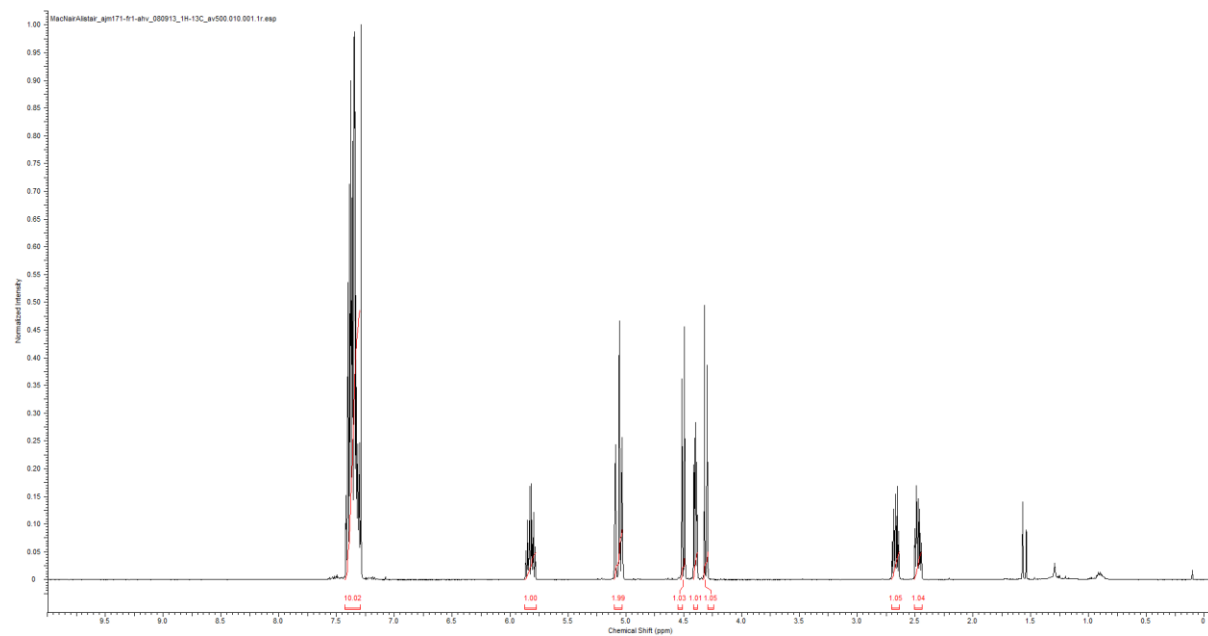
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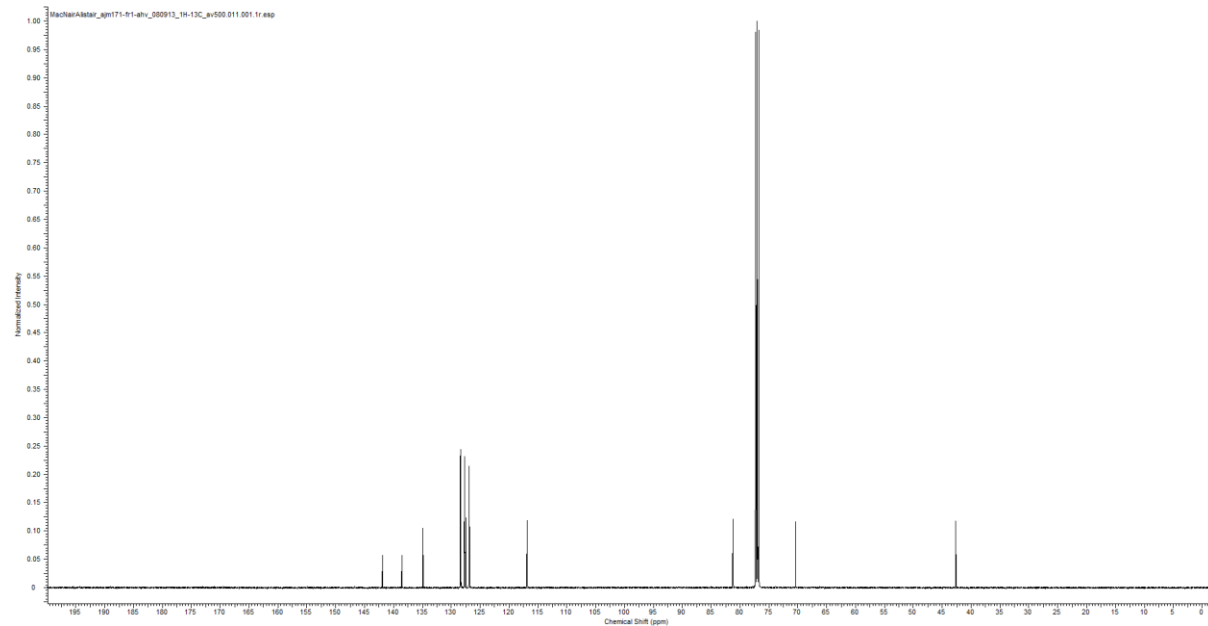
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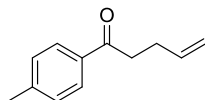
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



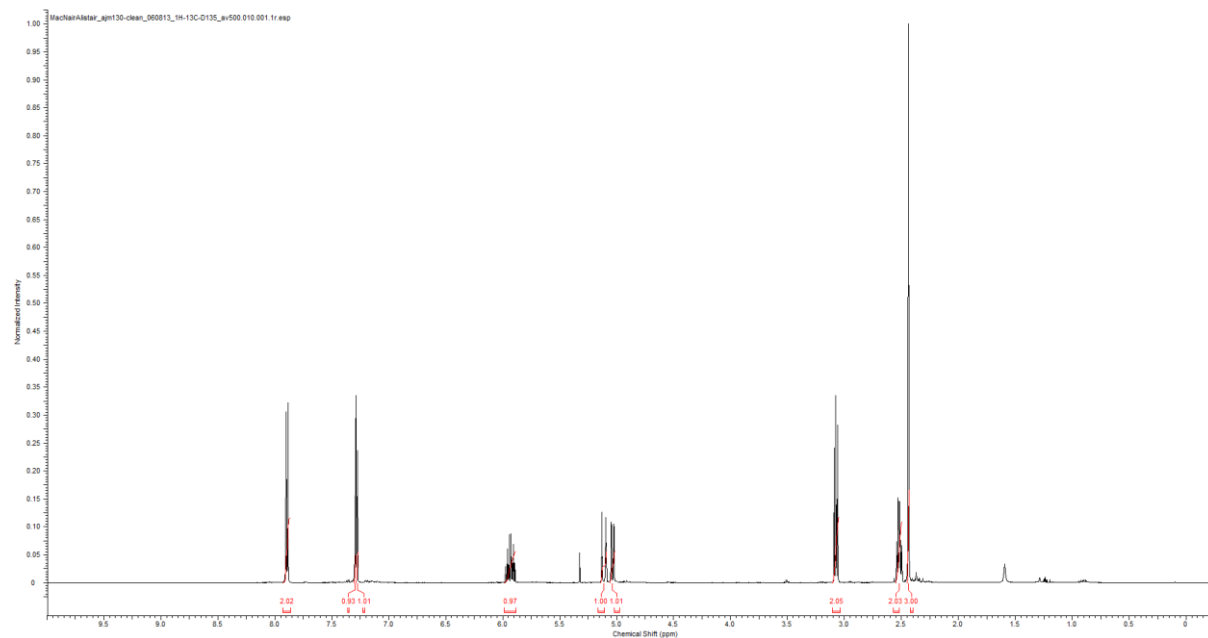
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



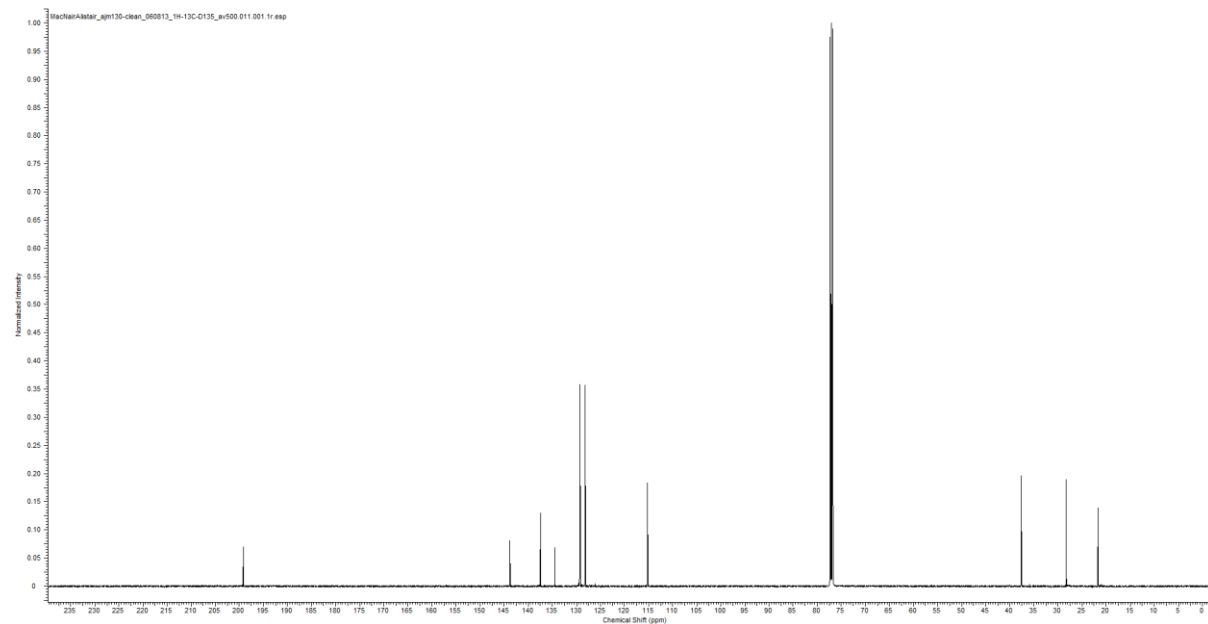
# 1-(4-Methylphenyl)-4-penten-1-one



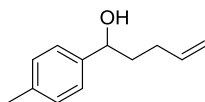
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



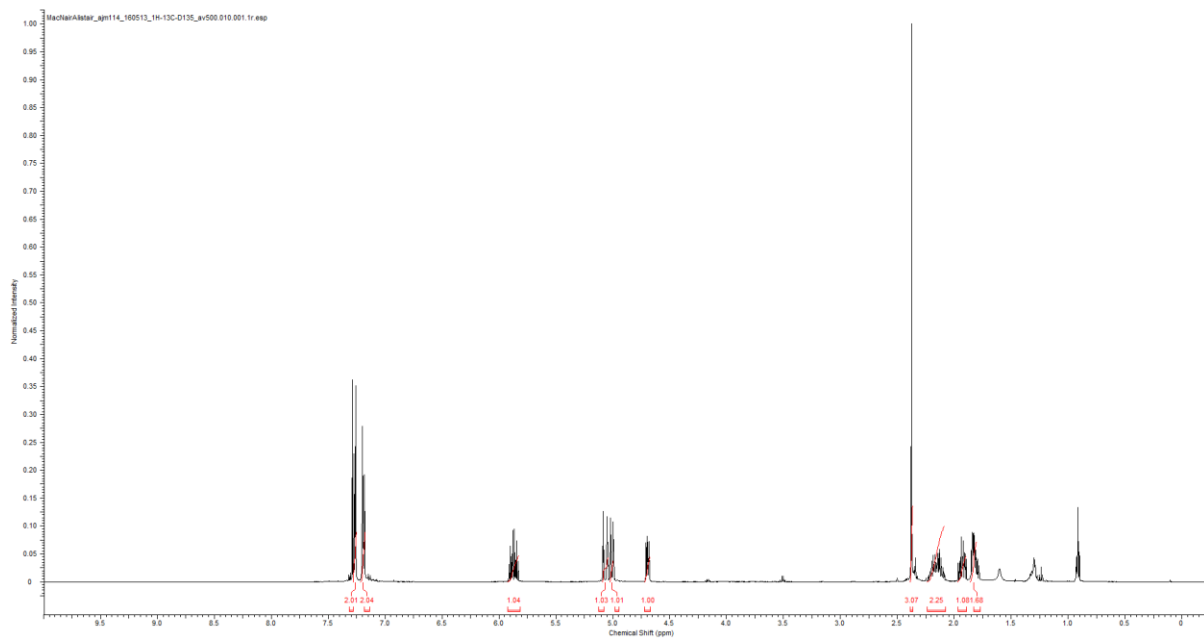
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



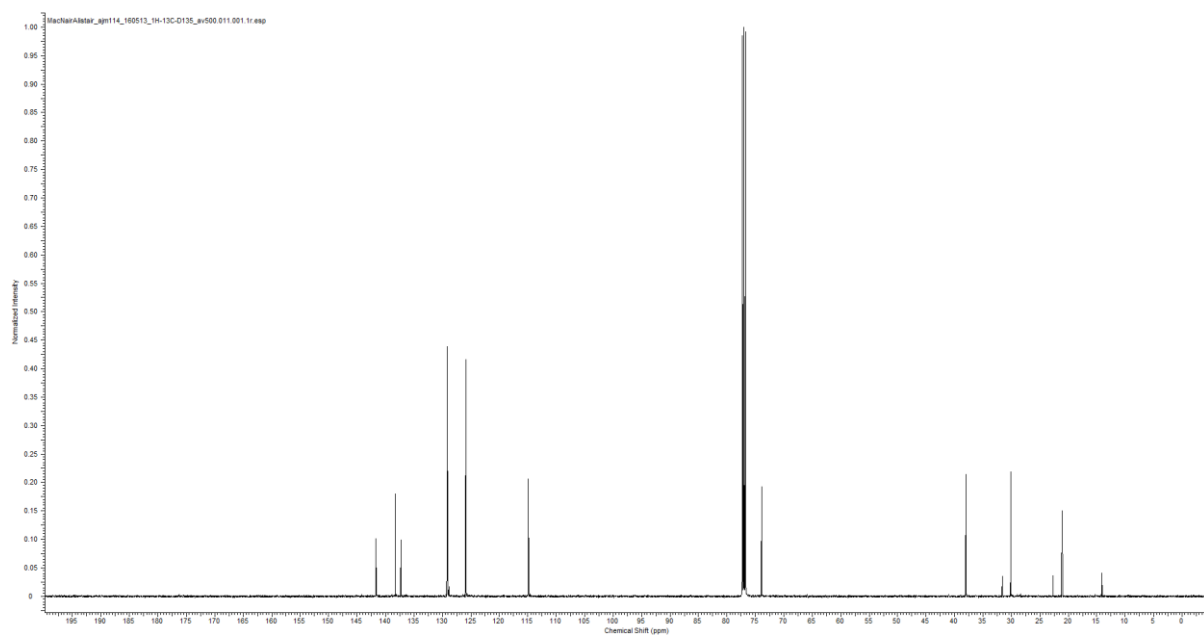
# 1-(4-Methylphenyl)-4-penten-1-ol



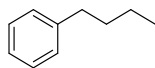
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



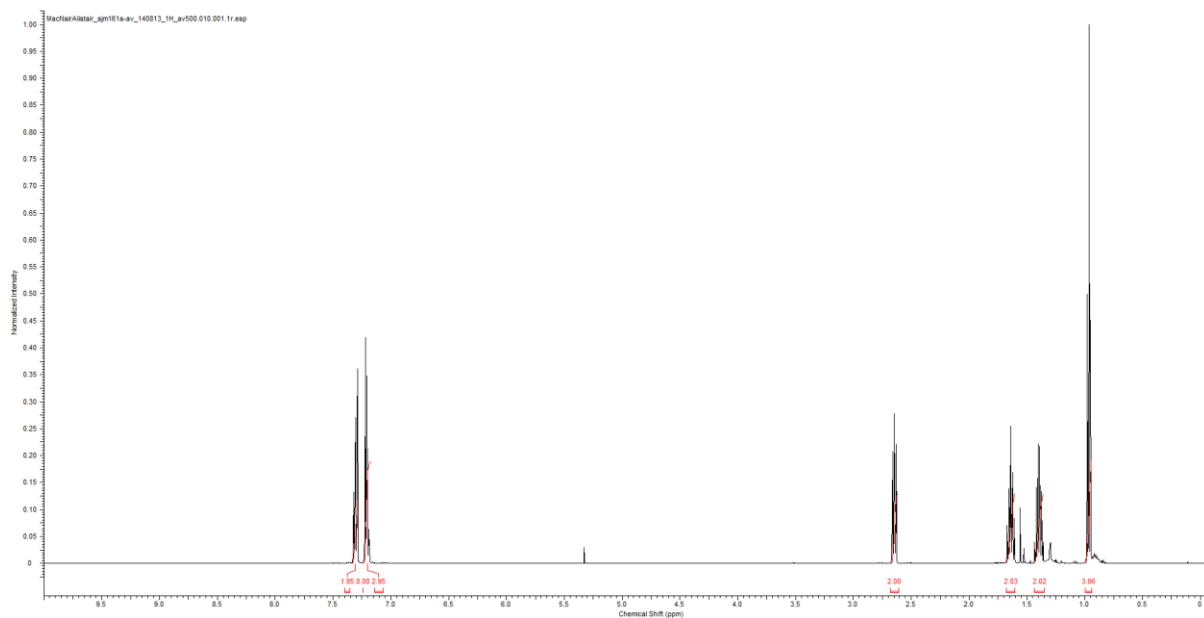
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



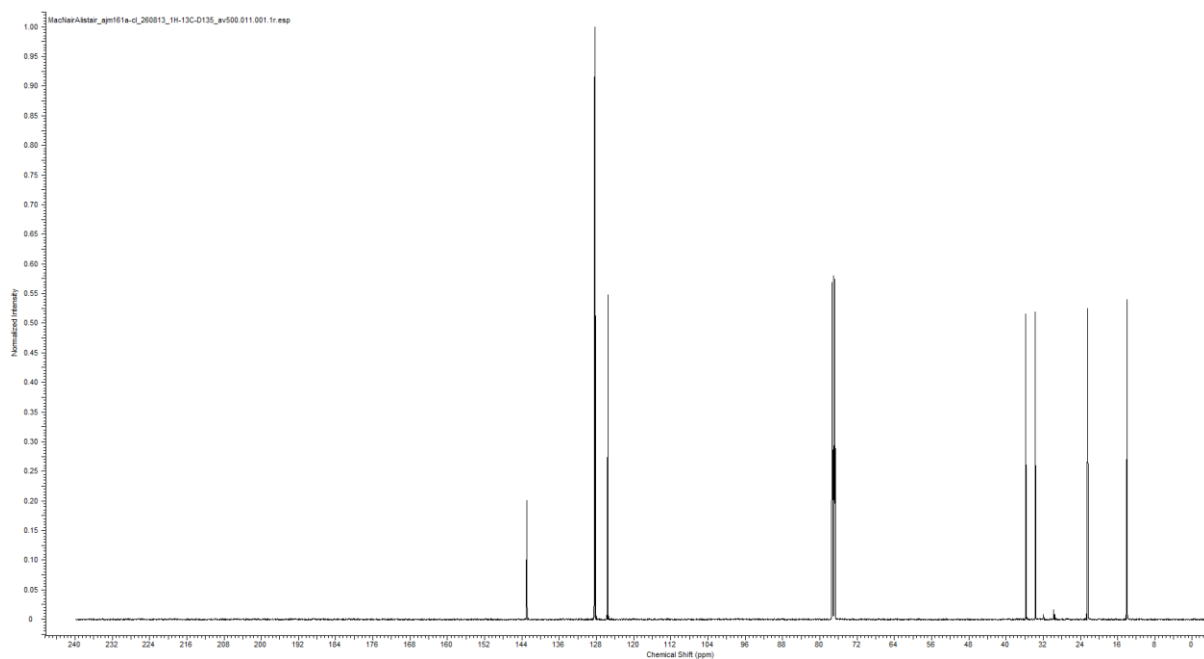
## Butylbenzene (66)



$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$

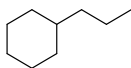


$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$

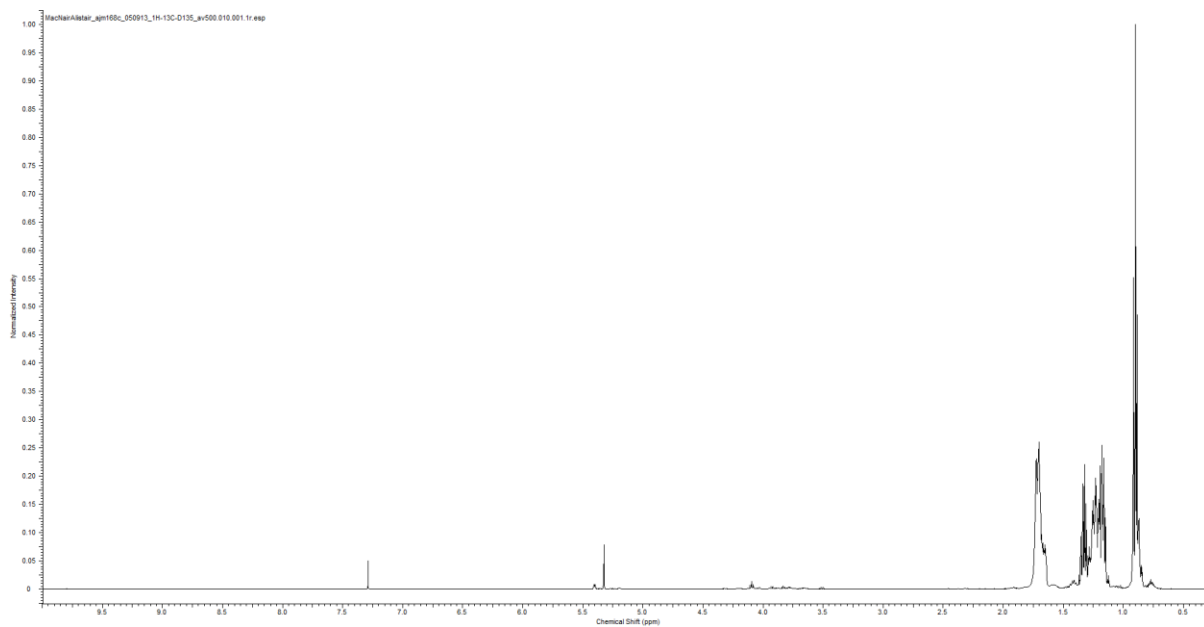




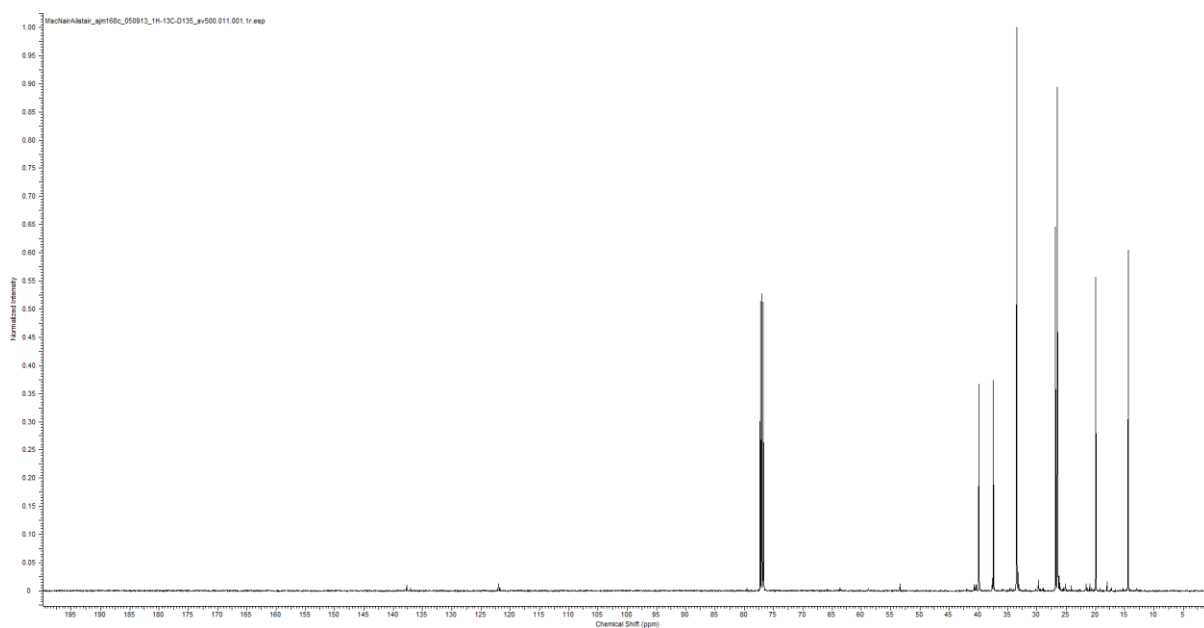
## Propylcyclohexane (75)



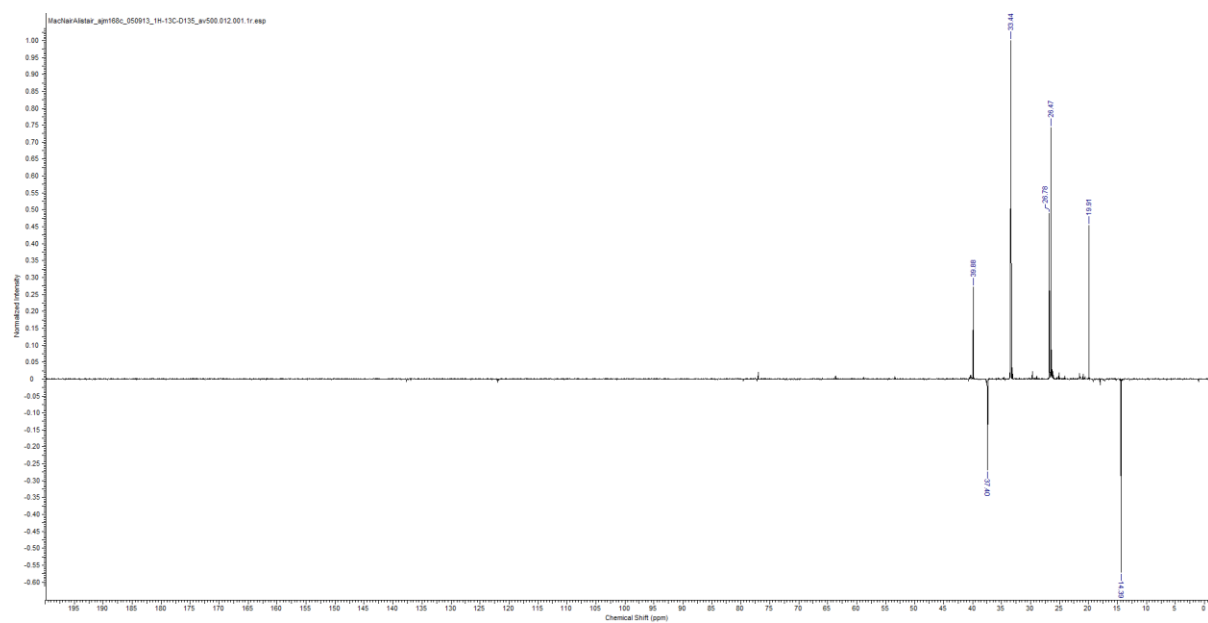
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



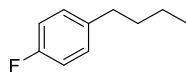
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



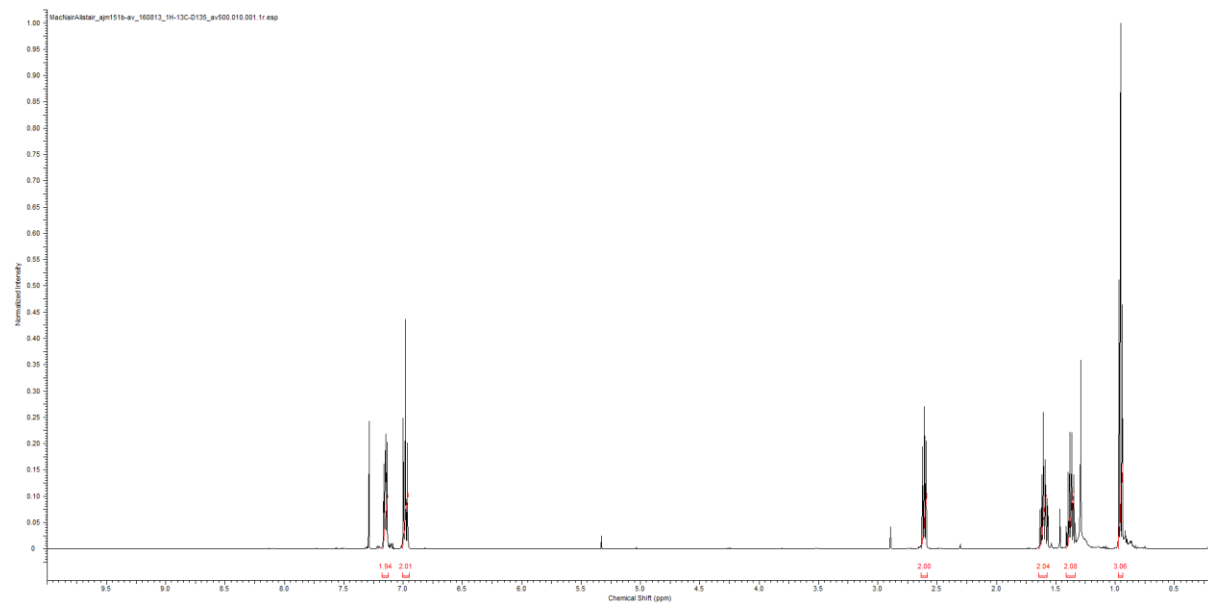
DEPT135, 125 MHz, CDCl<sub>3</sub>



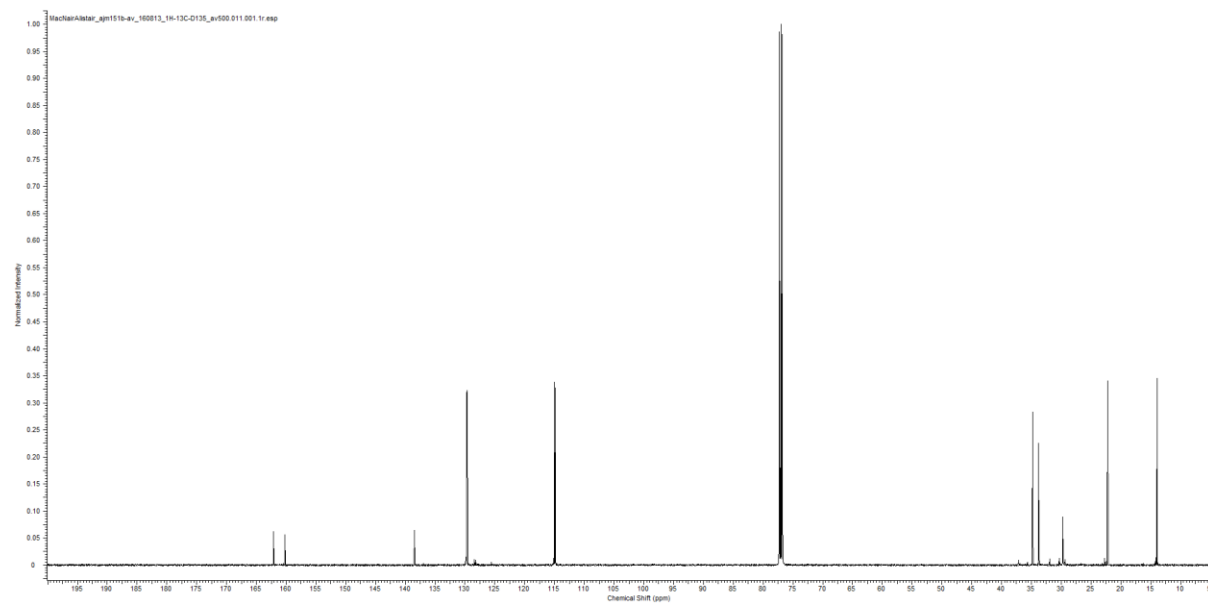
## 1-Fluoro-4-butylbenzene (81)



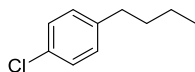
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



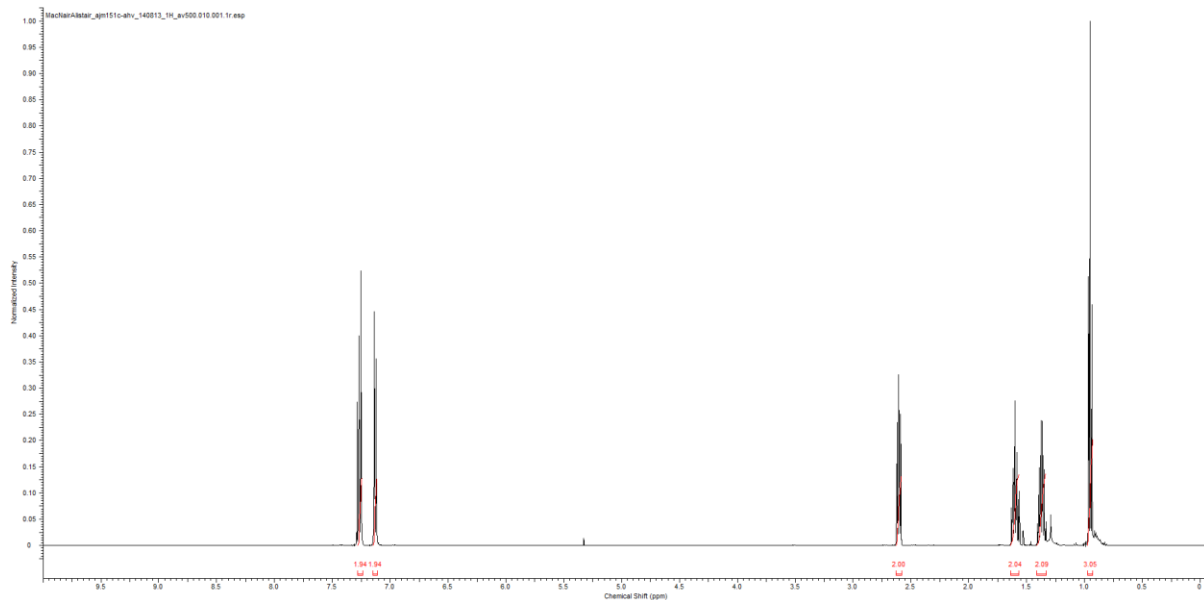
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



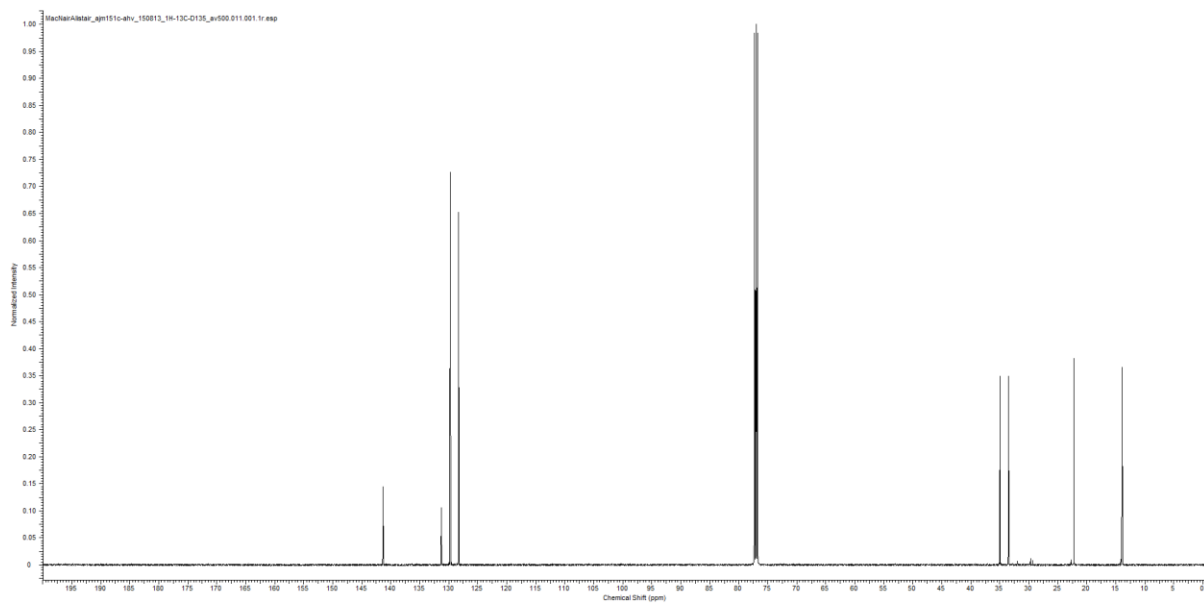
## 1-Chloro-4-butylbenzene (82)



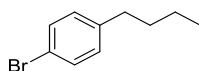
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



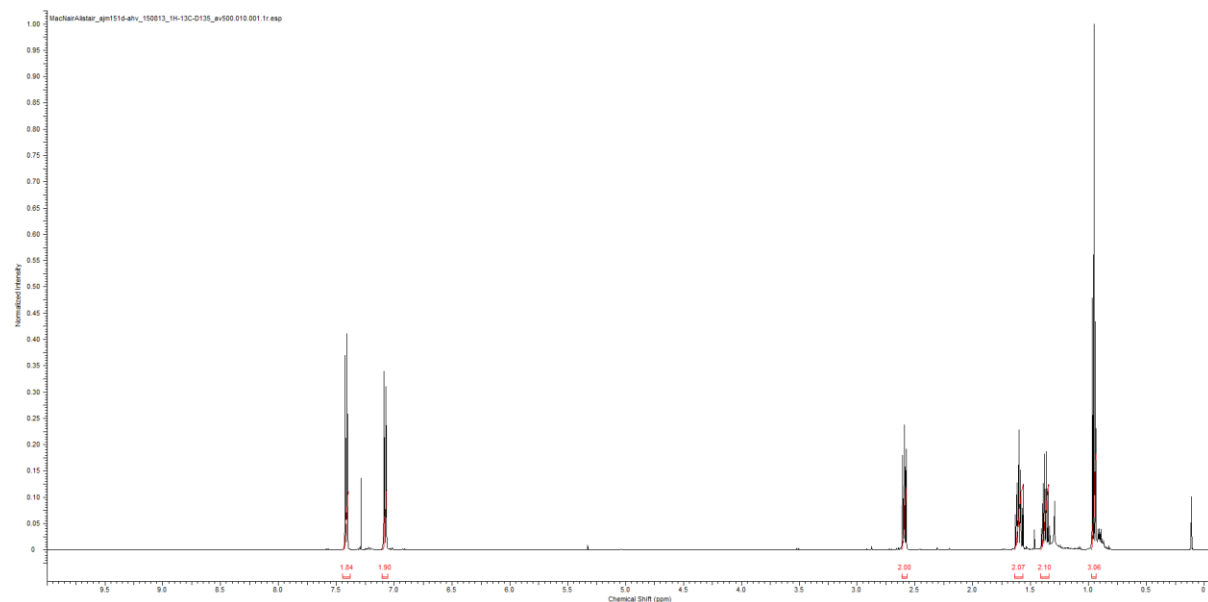
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



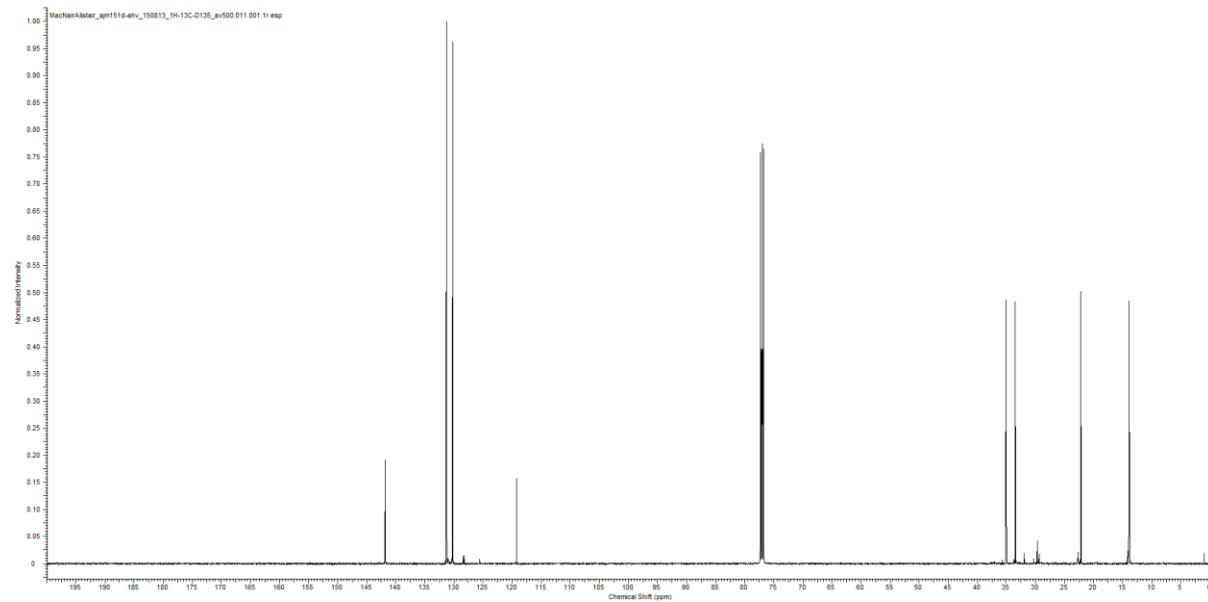
## 1-Bromo-4-butylbenzene (83)



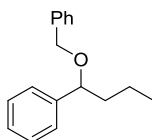
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



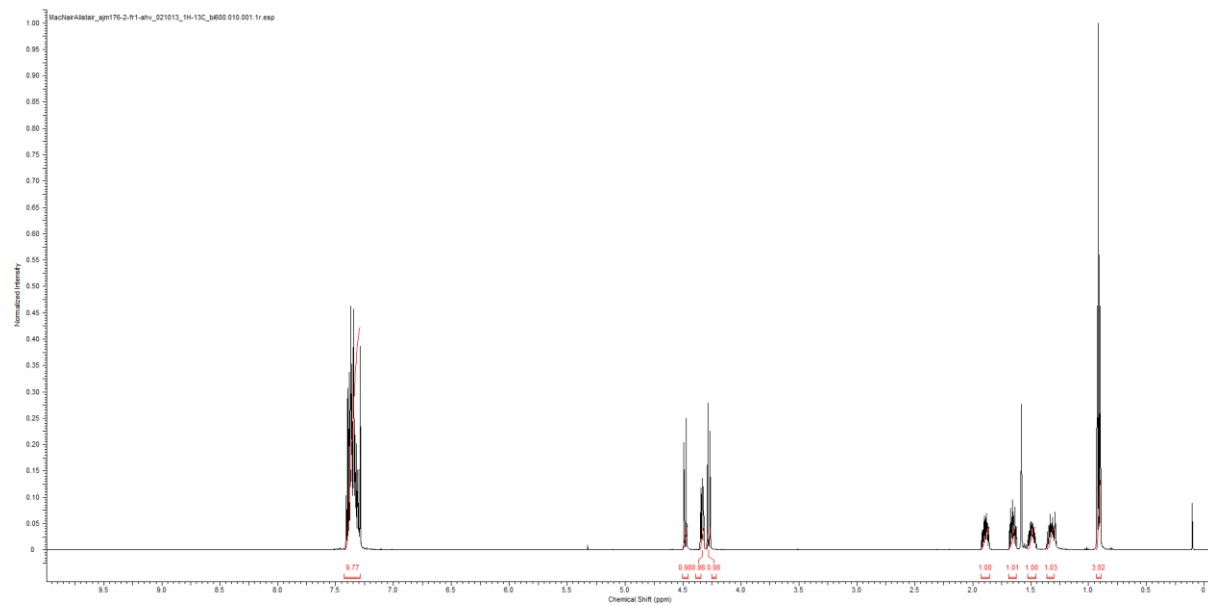
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



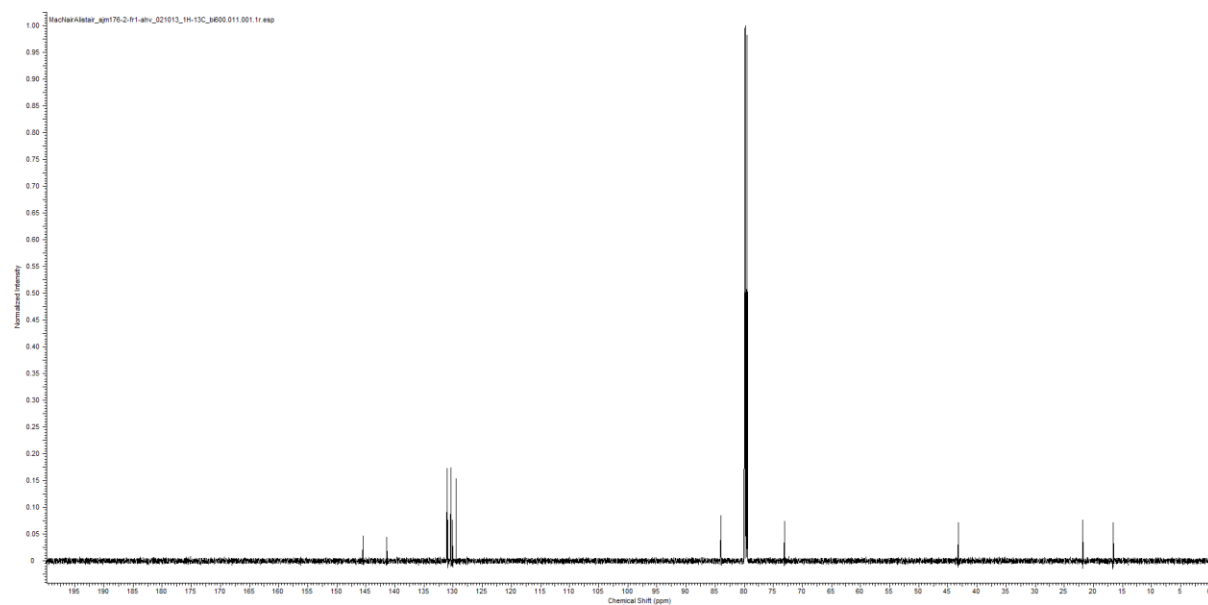
## Benzyloxy-1-phenylbutane (88)



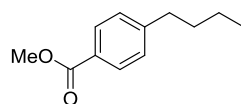
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



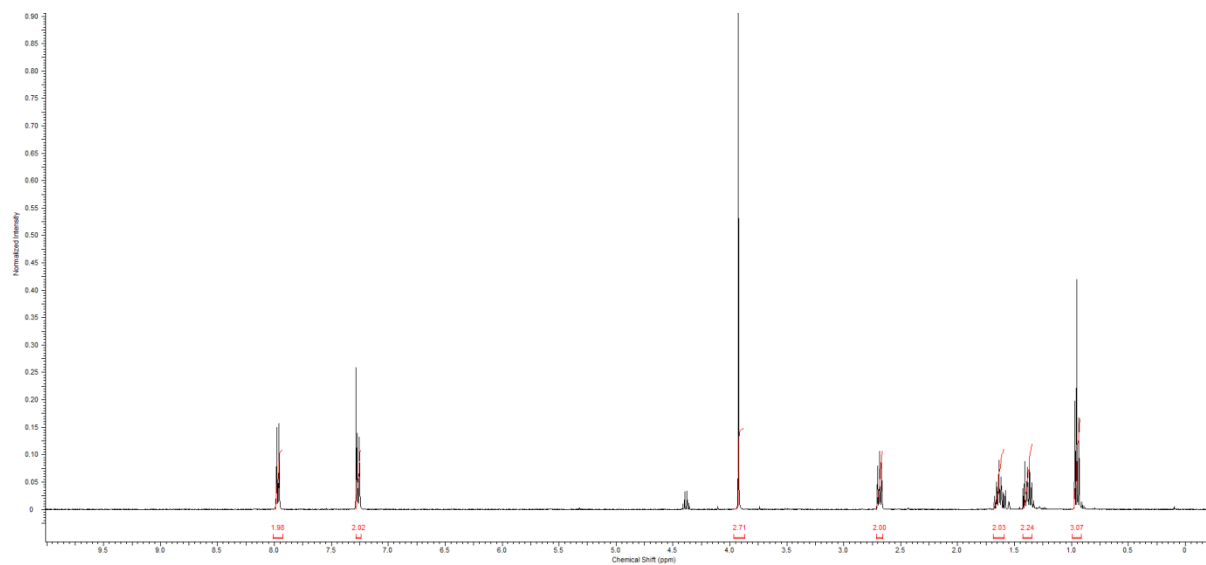
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



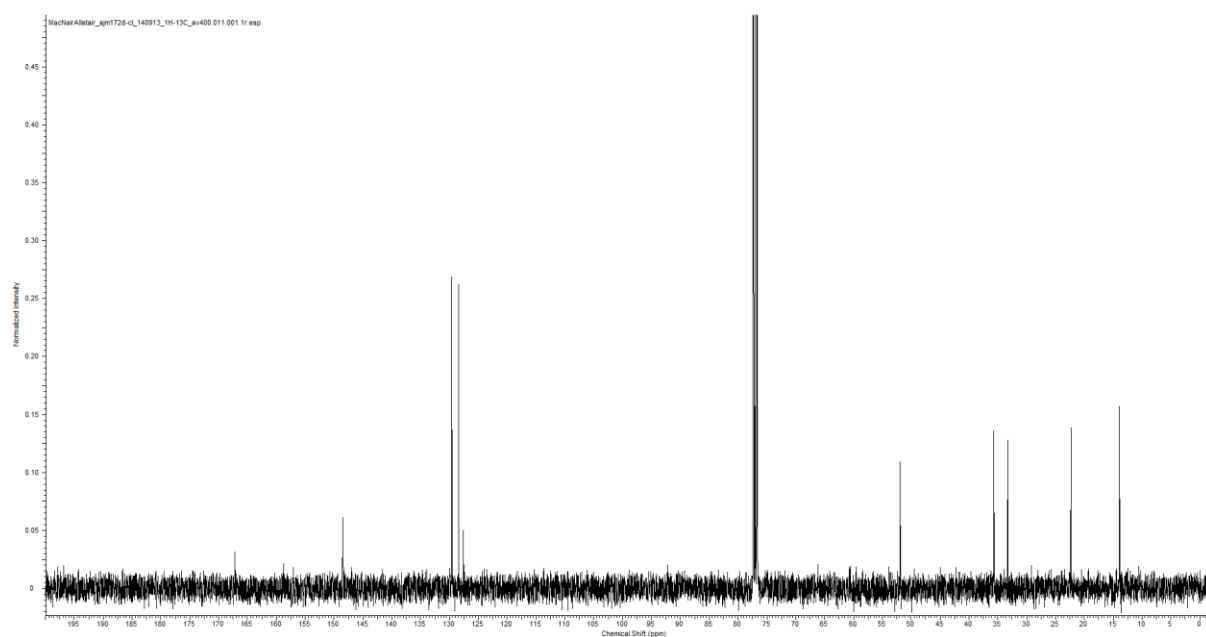
### 4-Butyl-benzoic acid, methyl ester (93)



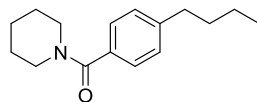
$^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



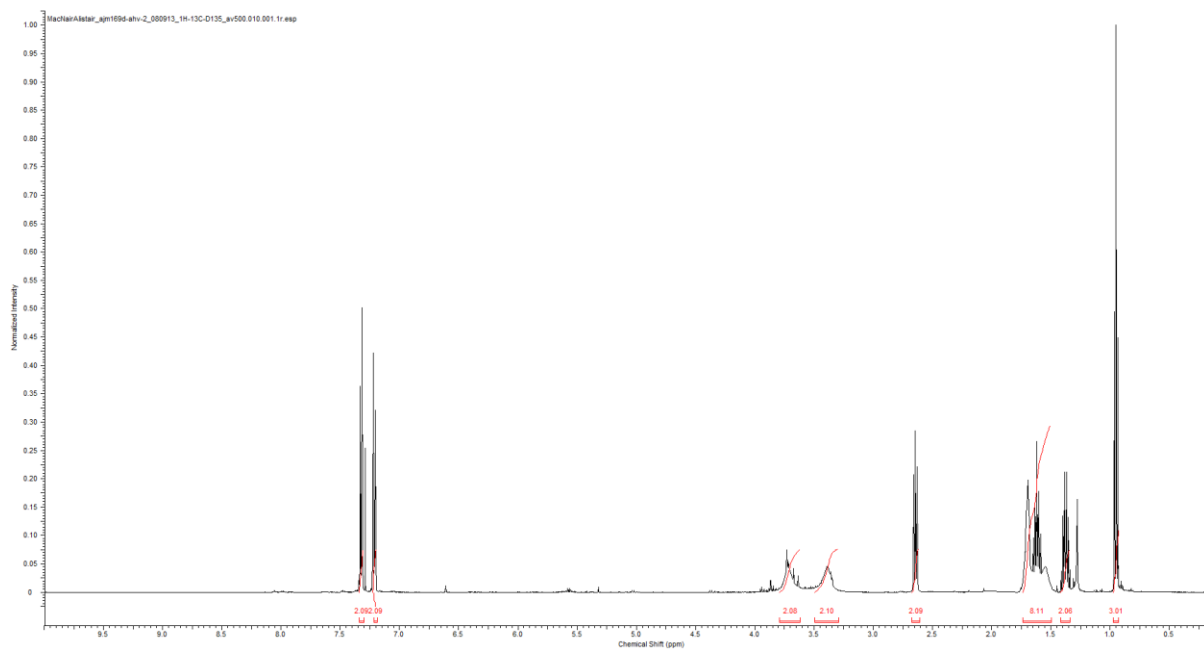
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



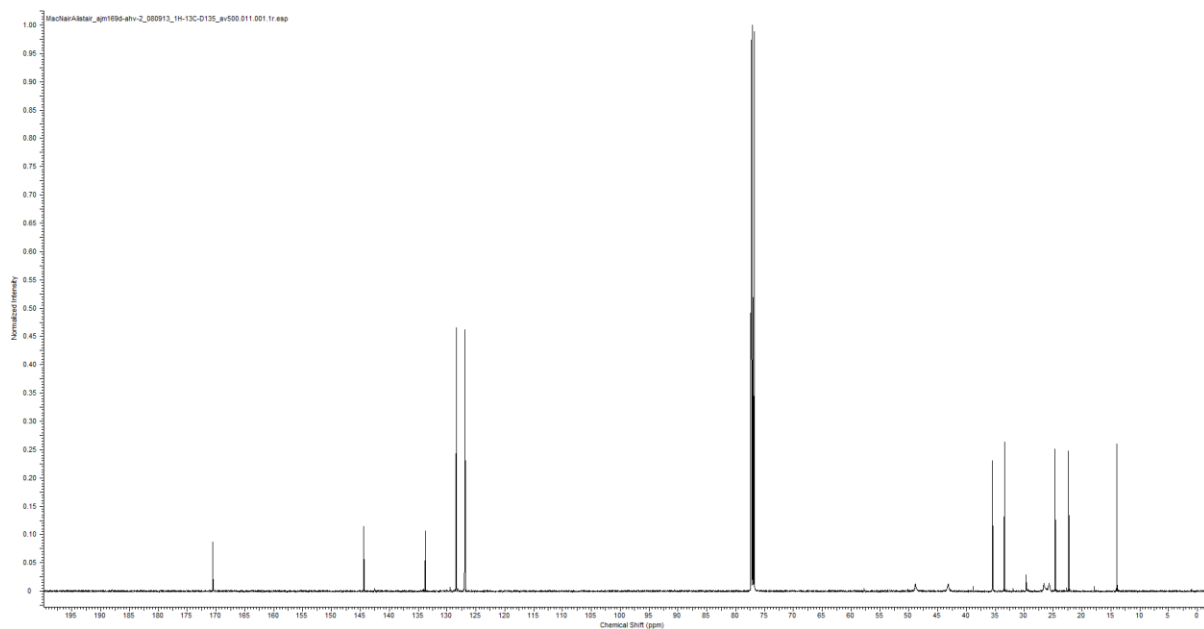
## 1-(4-Butylbenzoyl)-piperidine (95)



$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$

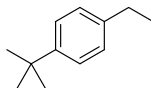


$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$

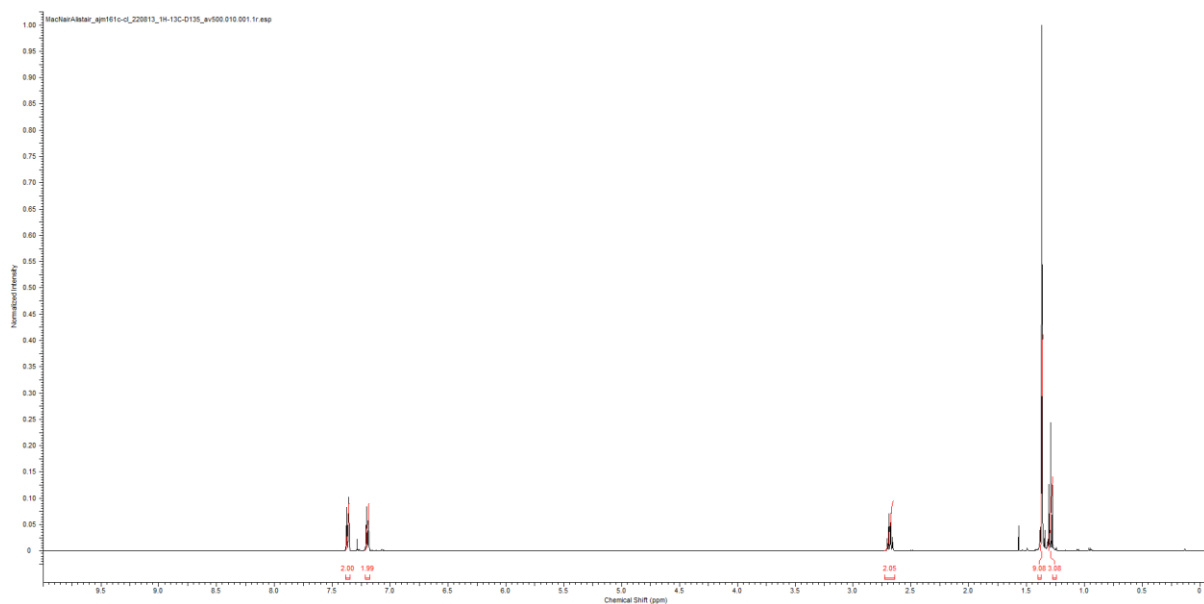




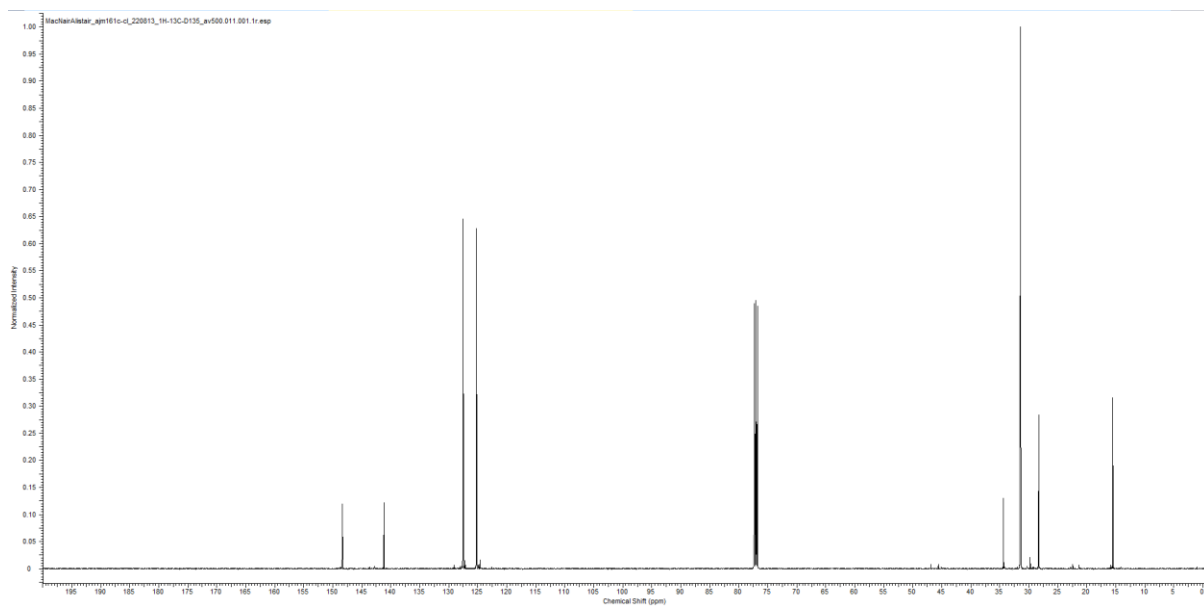
## 1-Ethyl-4-*tert*-butylbenzene (96)



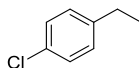
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



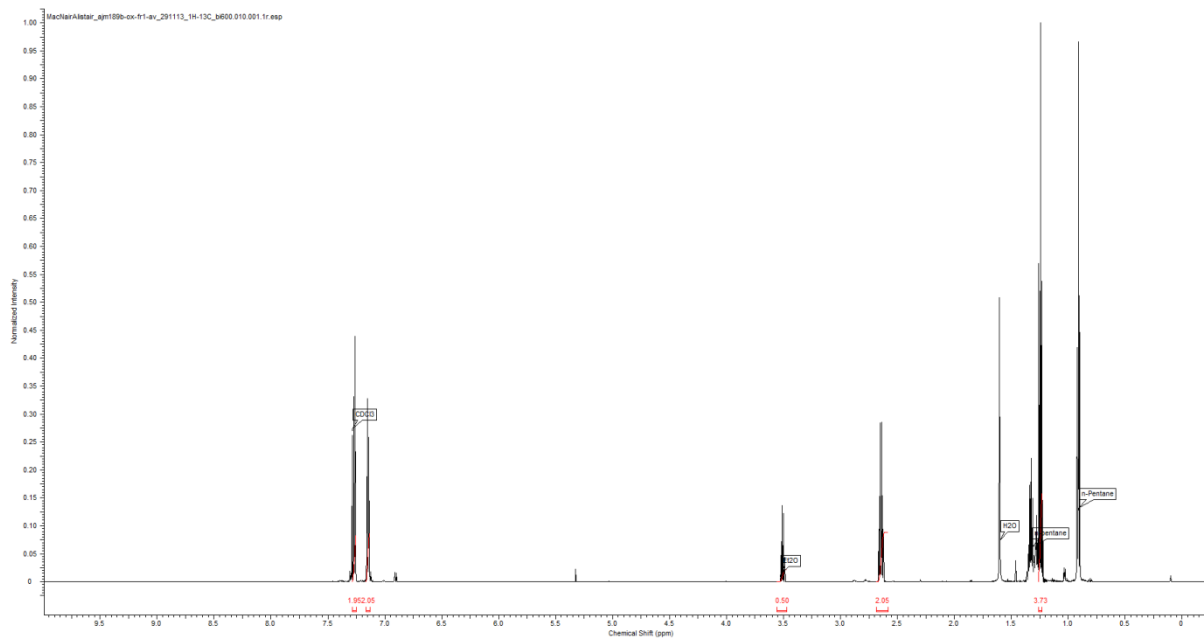
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



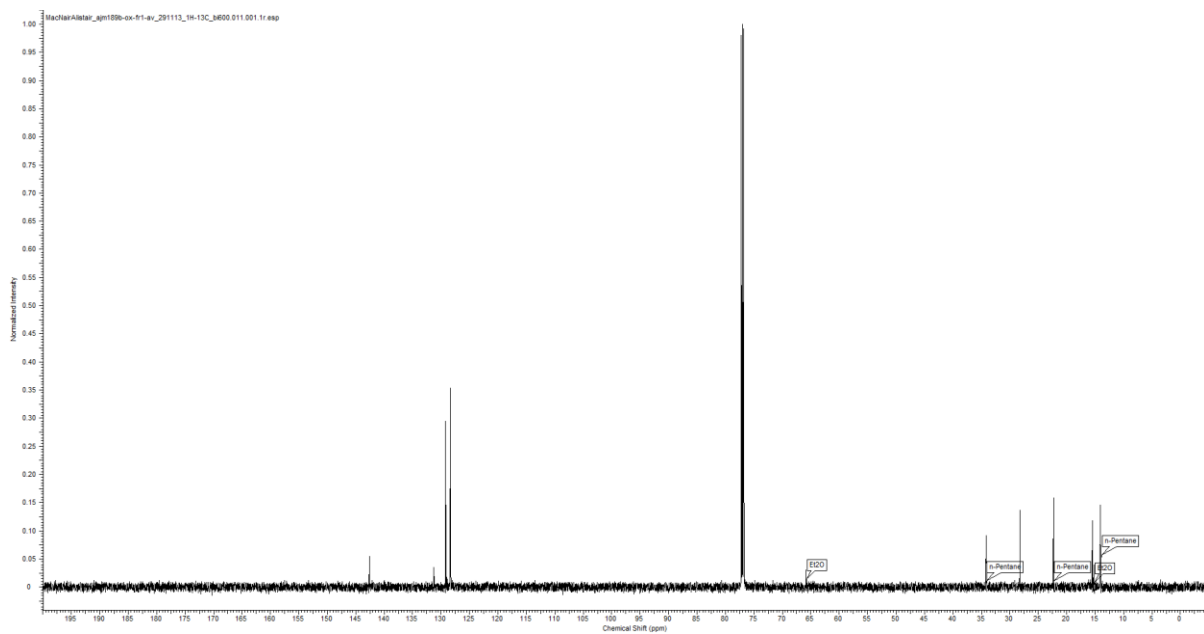
# 1-Ethyl-4-chlorobenzene (100)



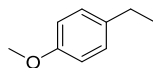
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



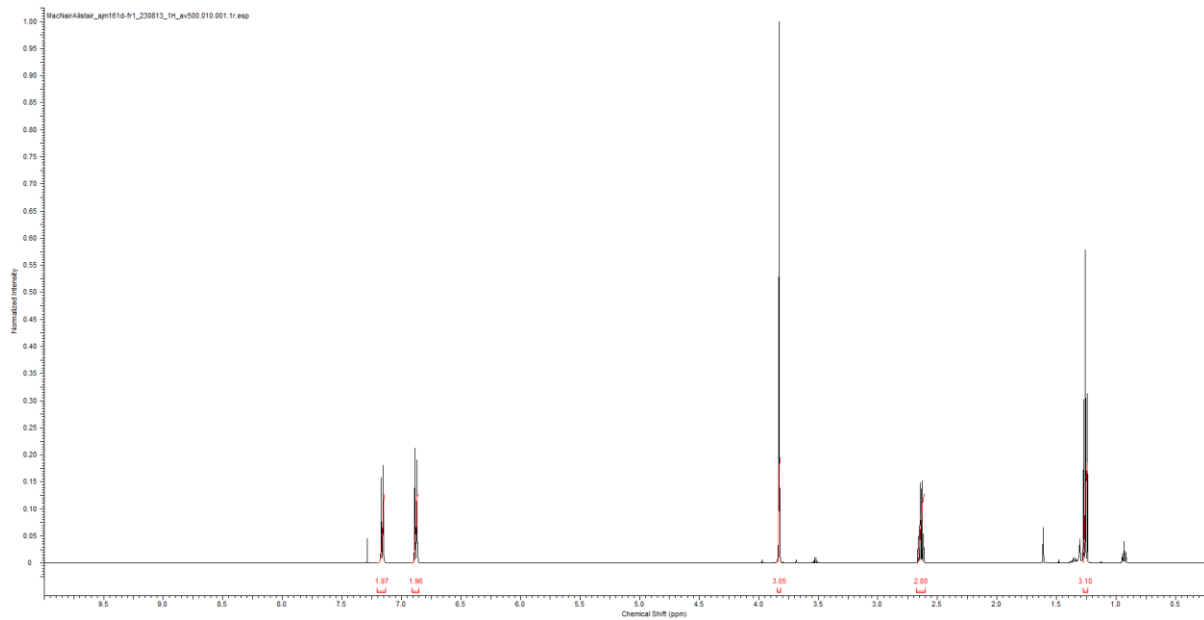
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



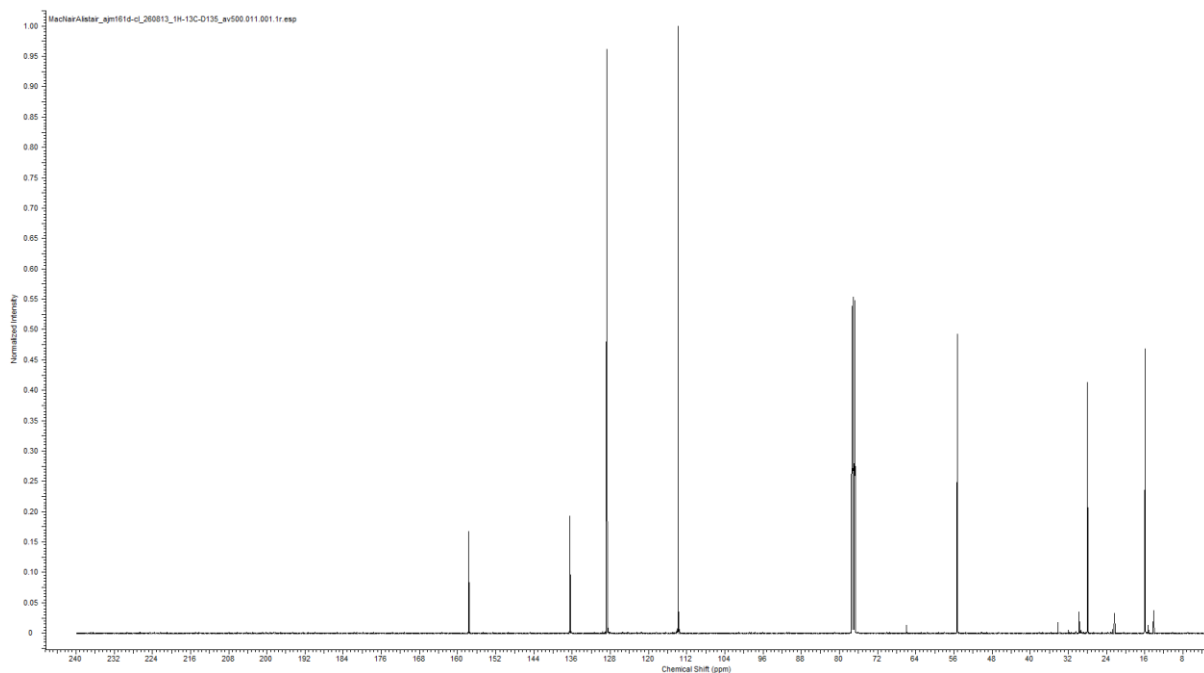
## 1-Ethyl-4-methoxybenzene (104)



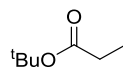
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



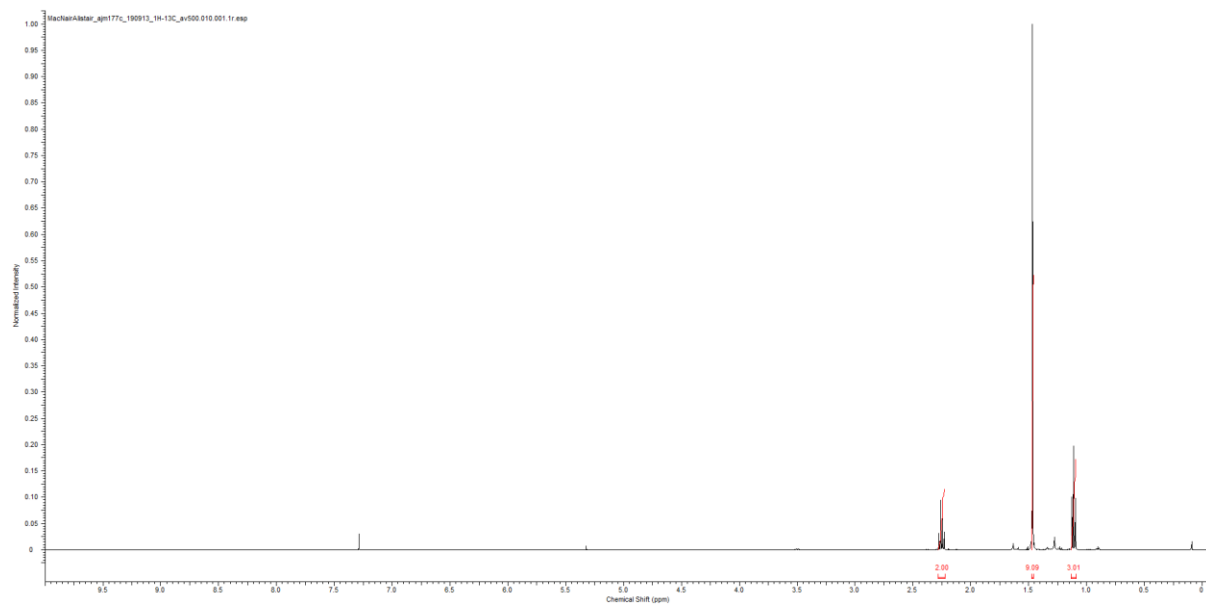
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



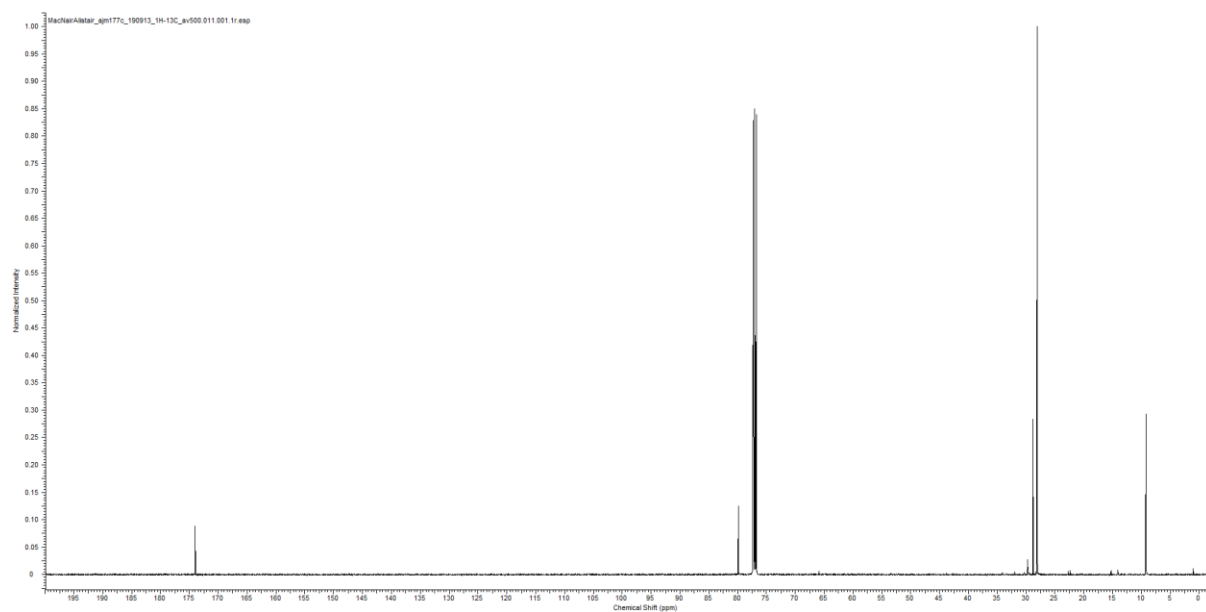
***tert*-Butyl propionate (113)**



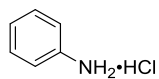
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



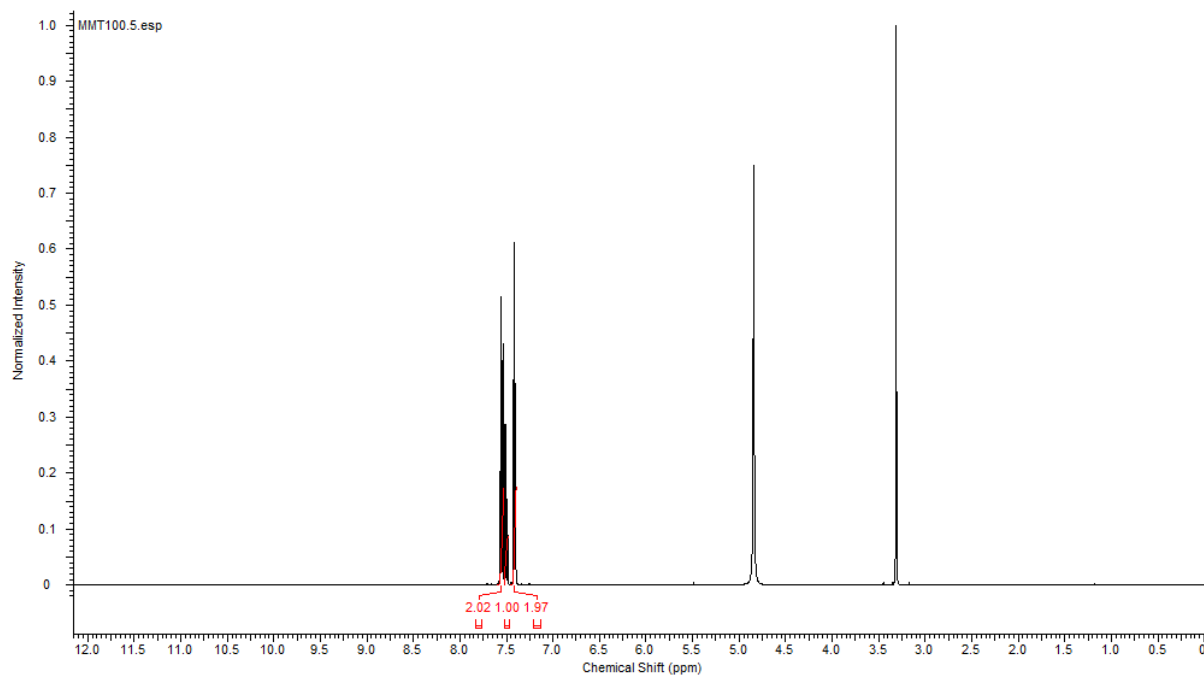
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



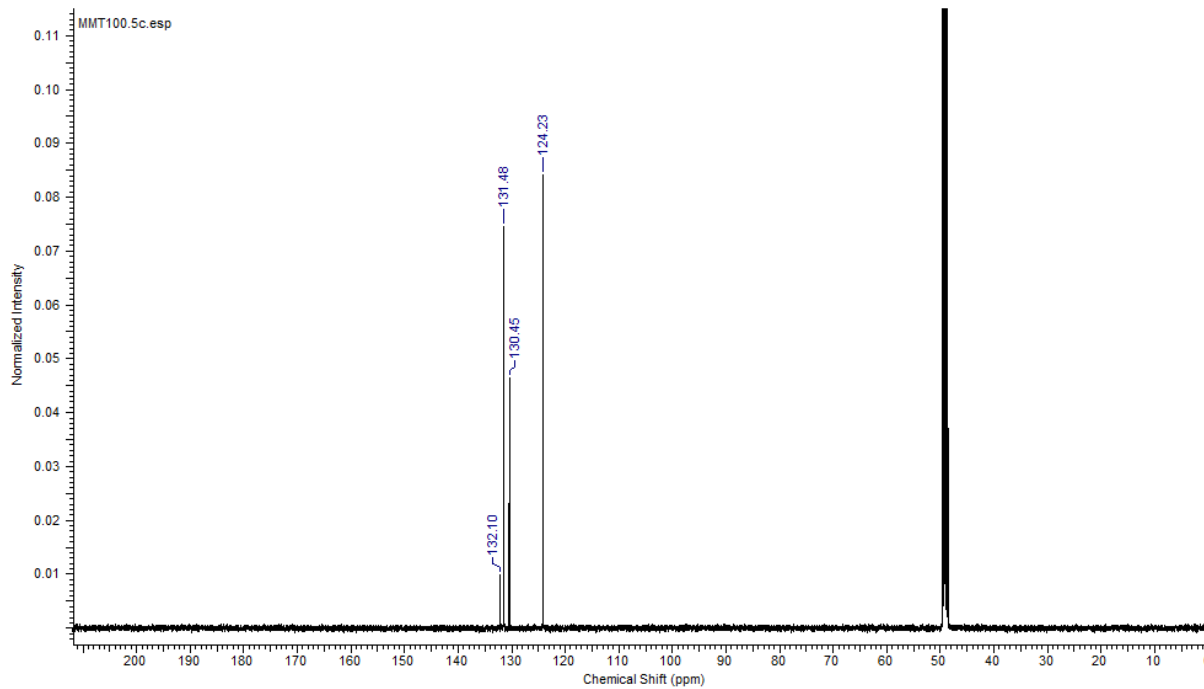
## Aniline hydrochloride (141)



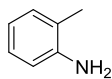
$^1\text{H}$ , 500 MHz,  $\text{CD}_3\text{OD}$



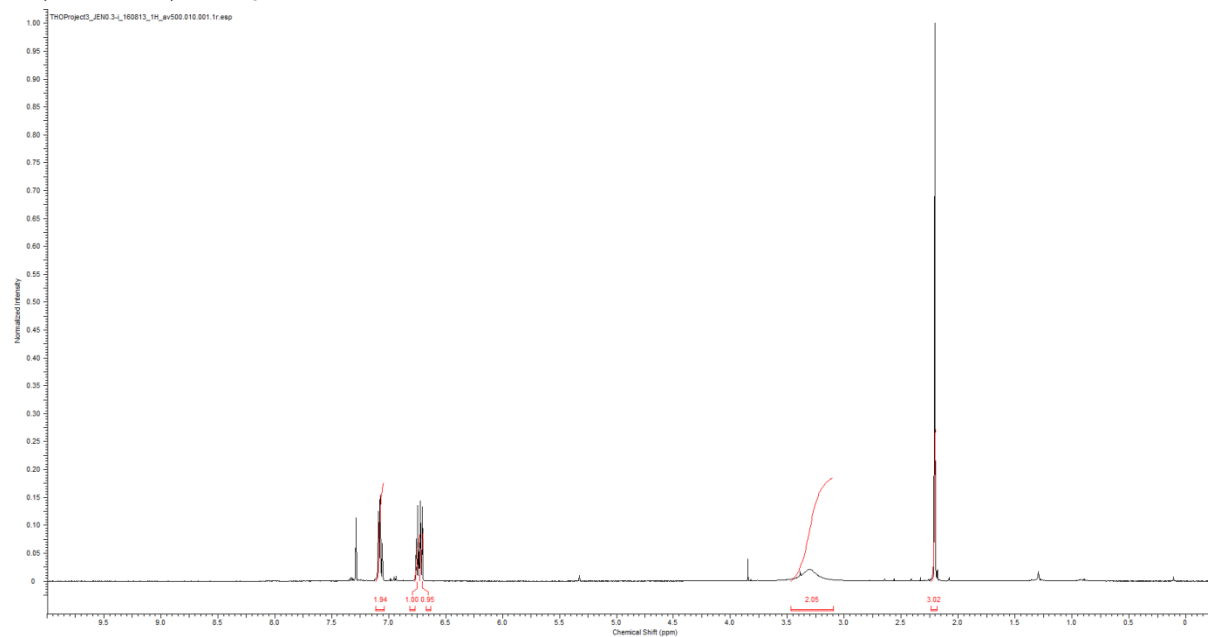
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_3\text{OD}$



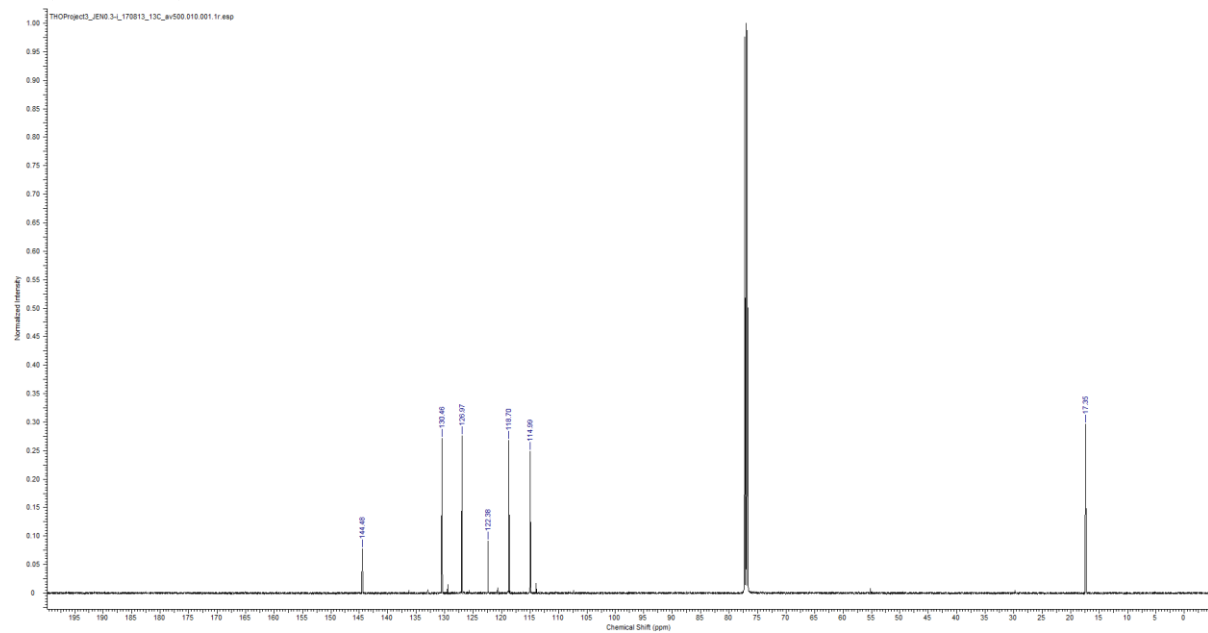
## 2-Aminotoluene (142)



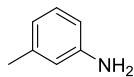
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



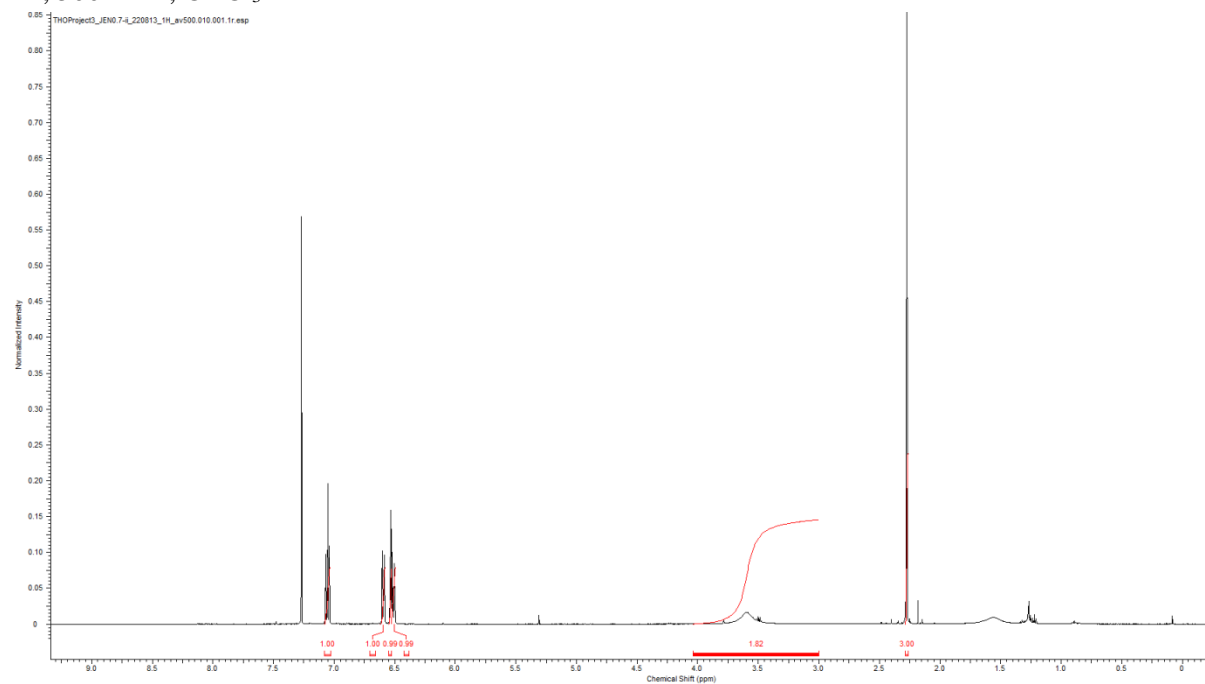
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



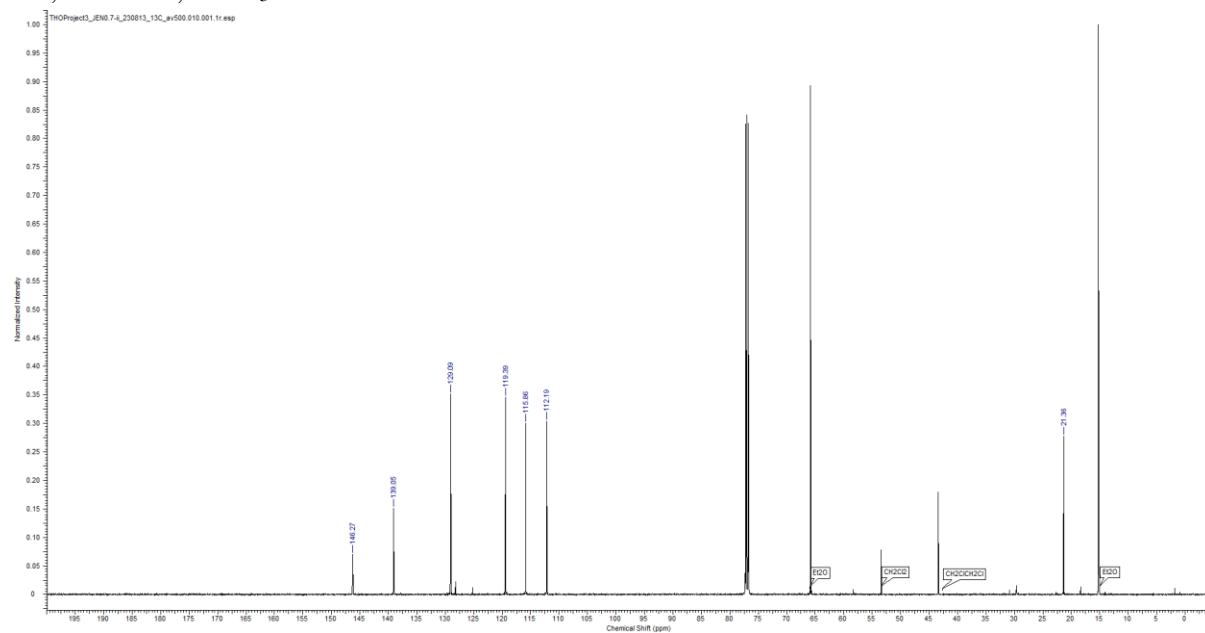
### 3-Aminotoluene (143)



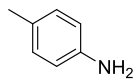
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



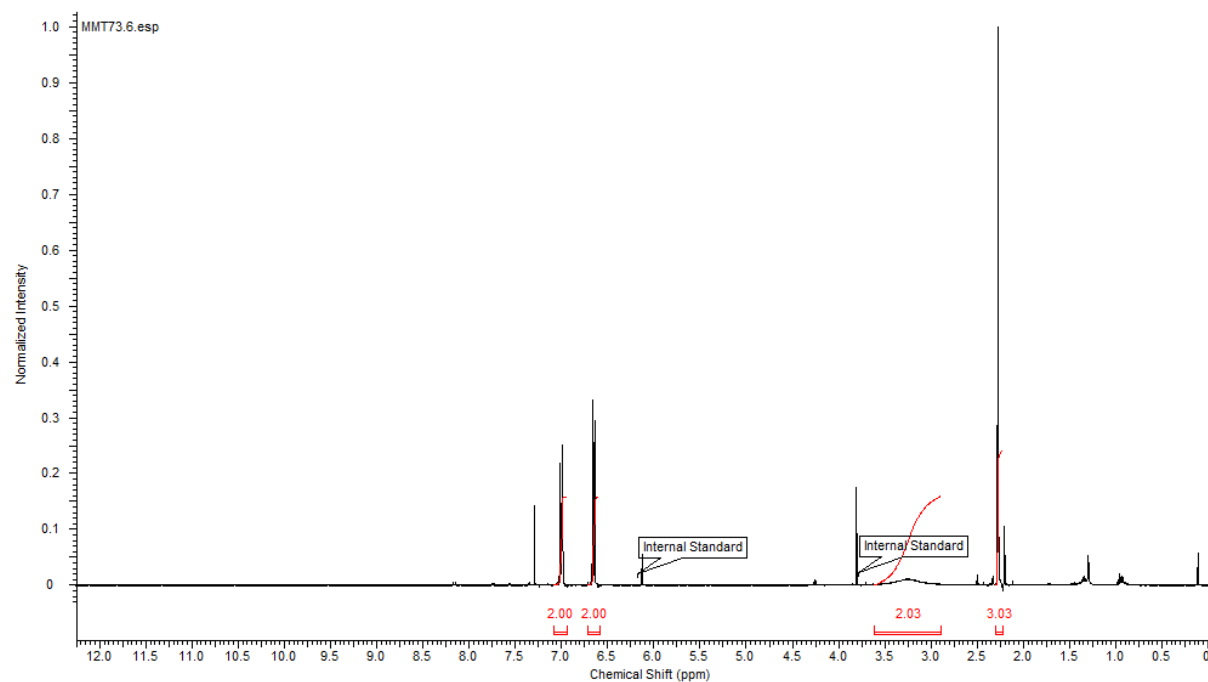
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



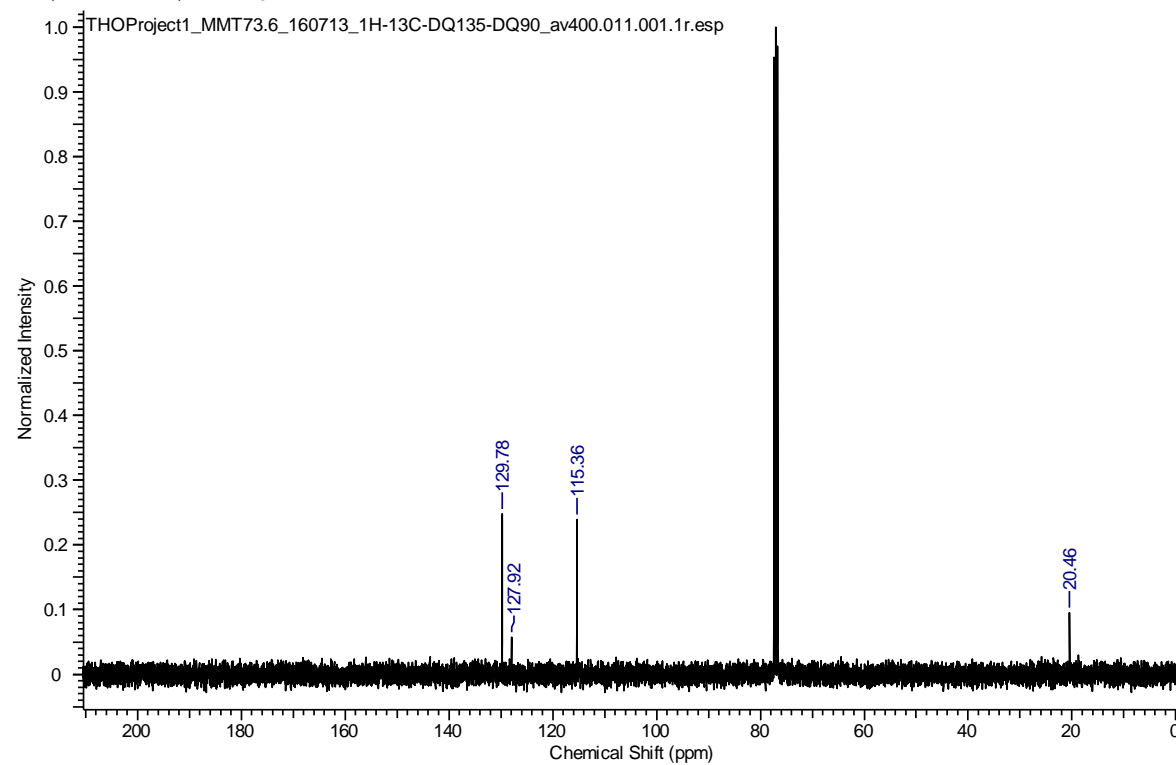
# 4-Aminotoluene (144)



$^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$

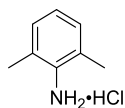


$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$

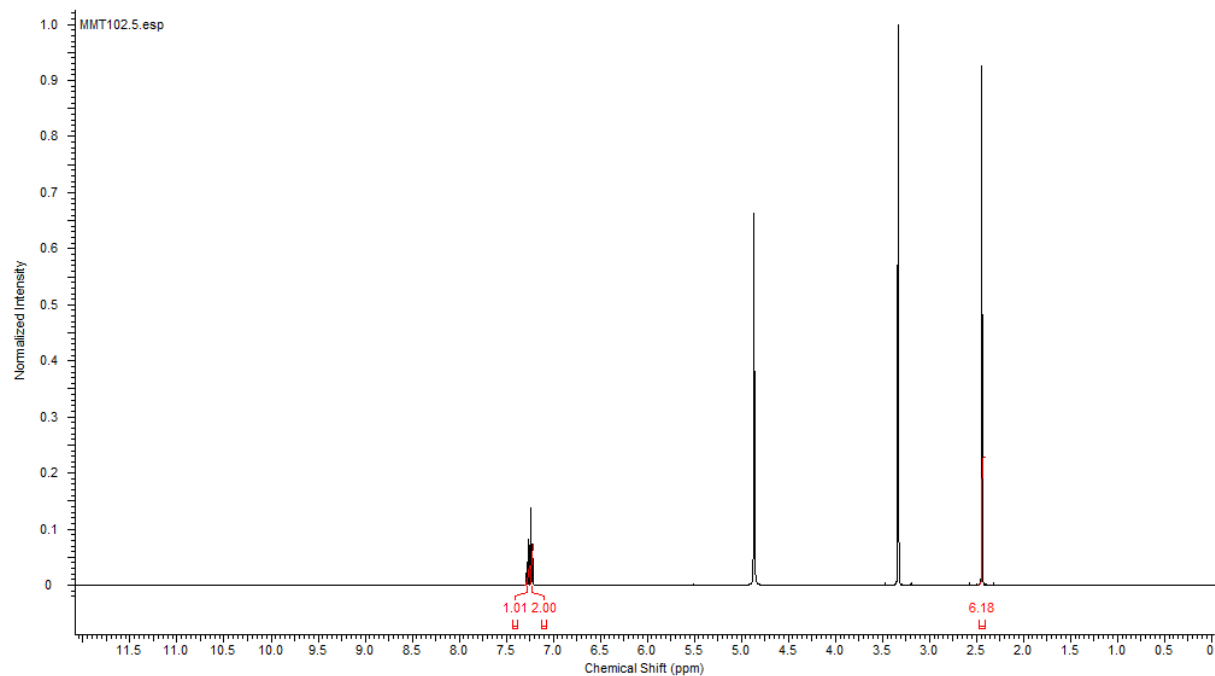




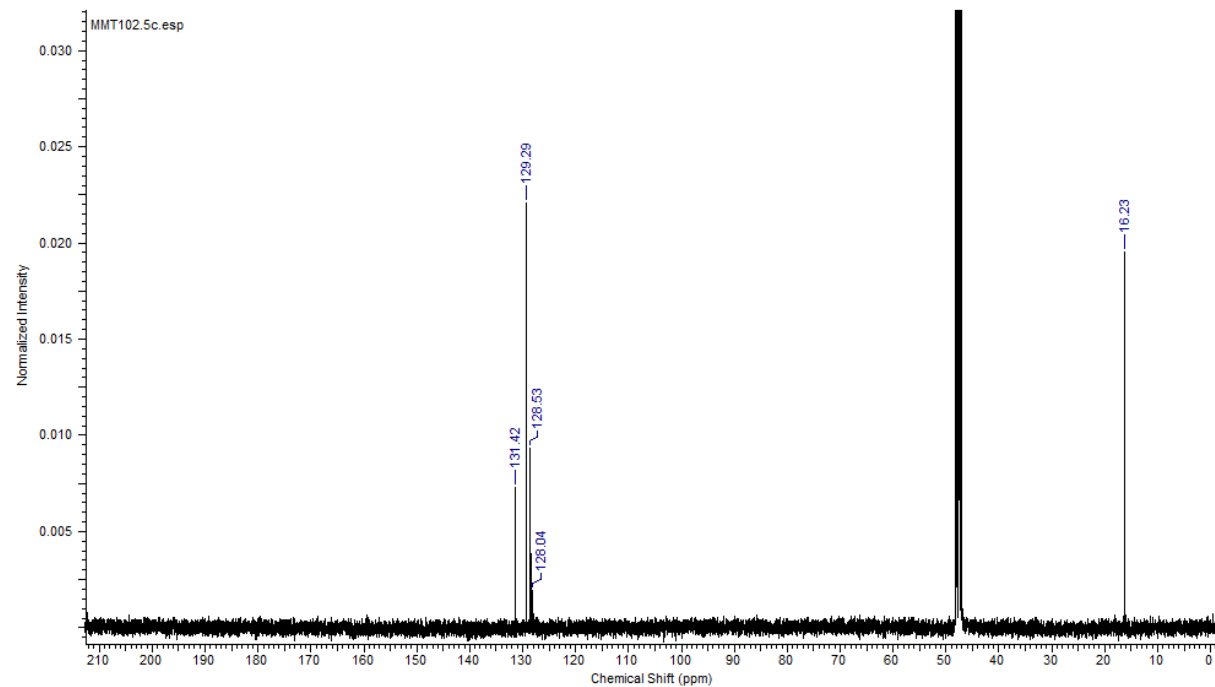
## 2,6-Dimethylaniline hydrochloride (145)



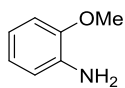
$^1\text{H}$ , 500 MHz,  $\text{CD}_3\text{OD}$



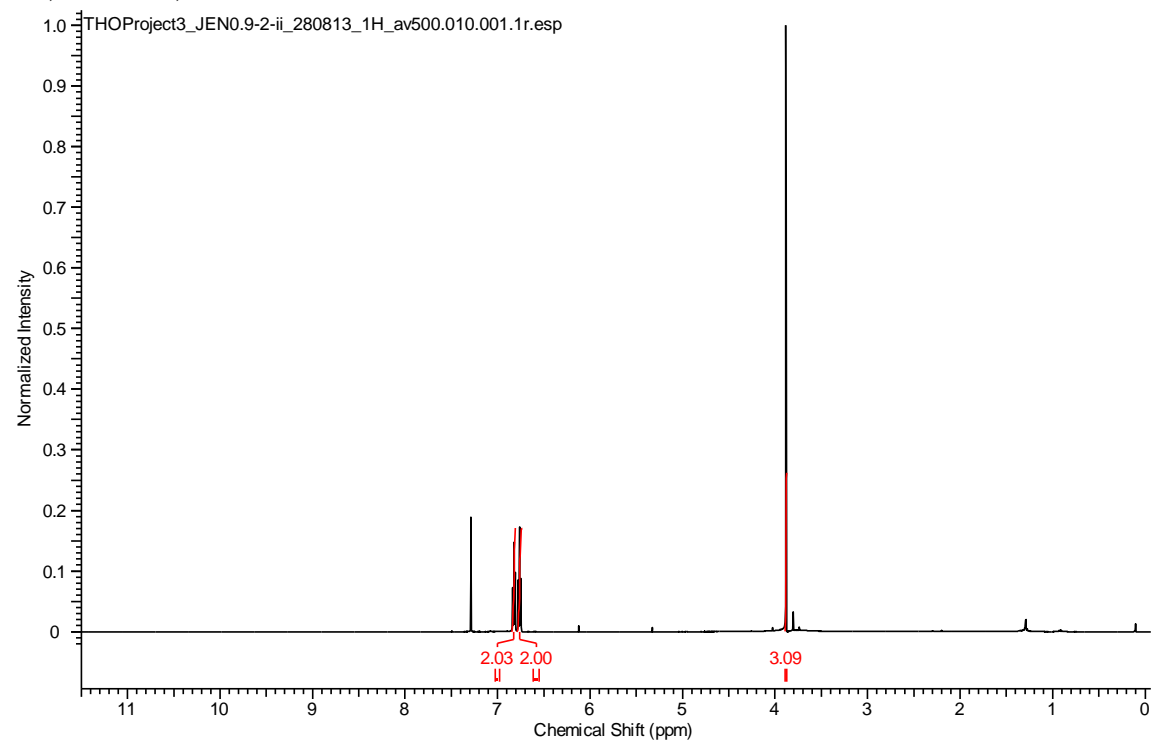
$^{13}\text{C}$ , 125 MHz,  $\text{CD}_3\text{OD}$



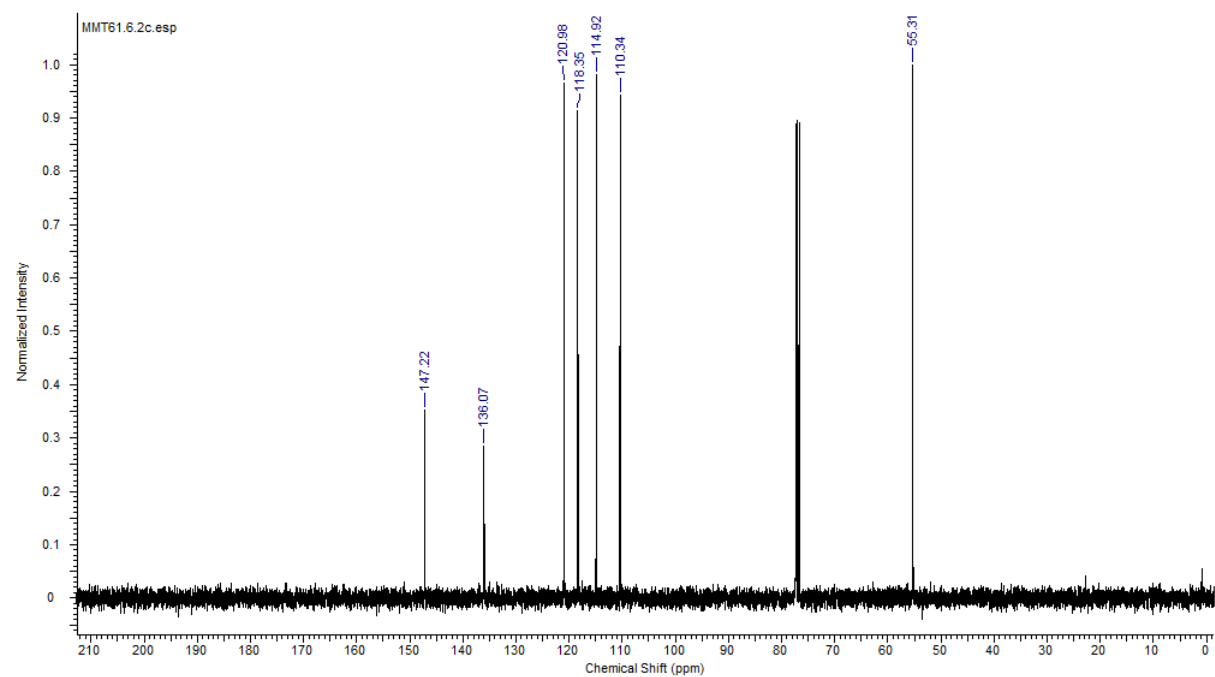
## 2-Methoxyaniline (145)



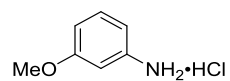
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



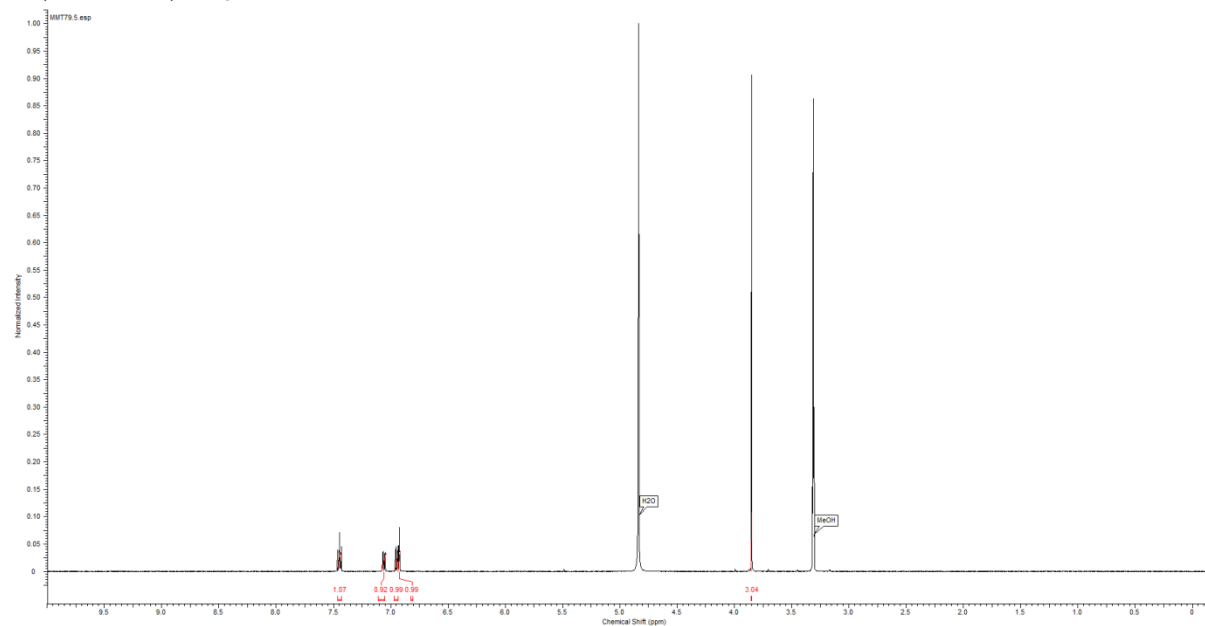
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



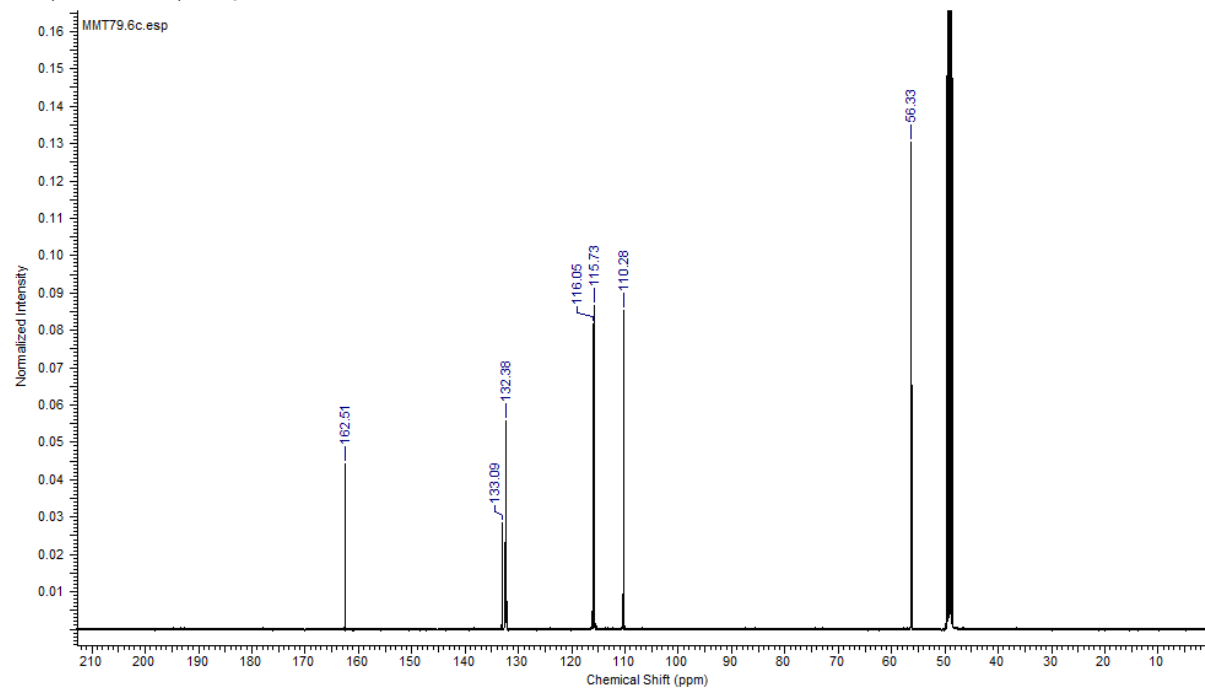
### 3-Methoxyaniline hydrochloride (147)



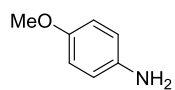
$^1\text{H}$ , 400 MHz,  $\text{CD}_3\text{OD}$



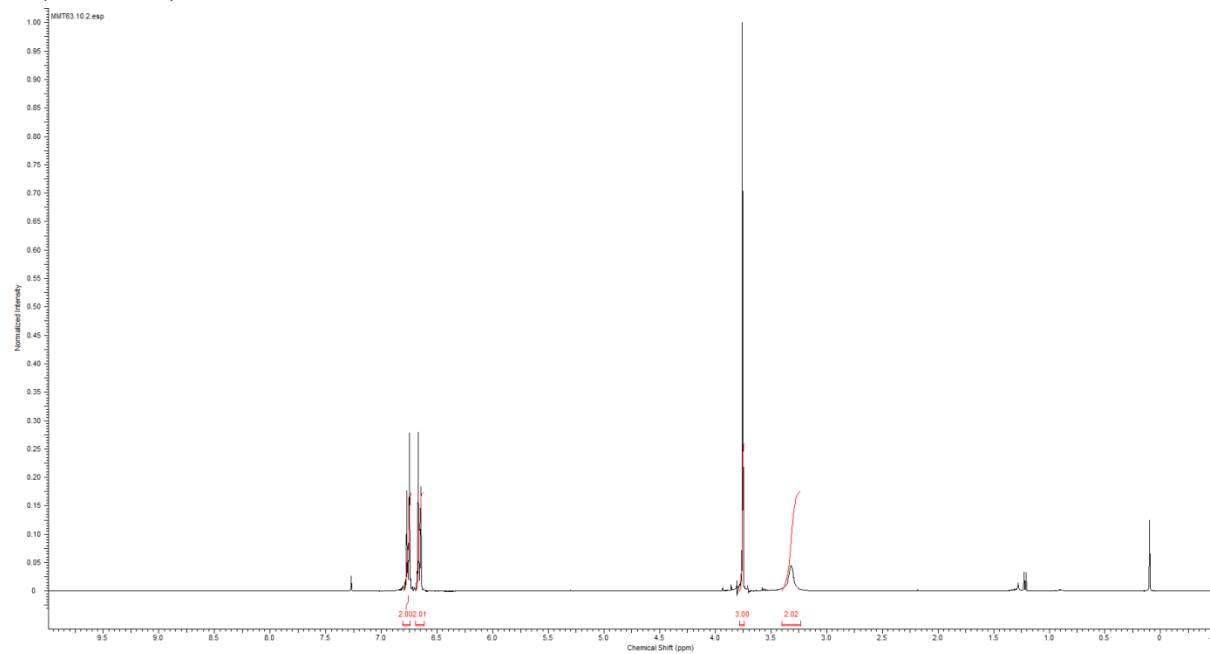
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_3\text{OD}$



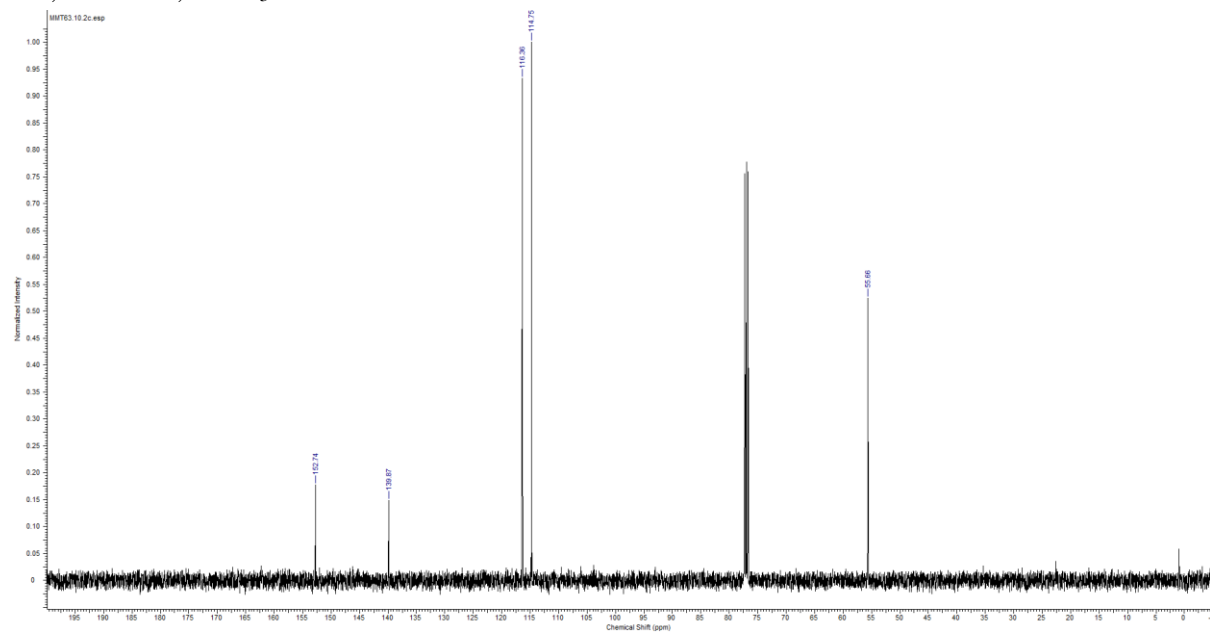
## 4-Methoxyaniline (148)



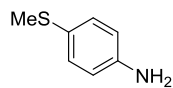
$^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



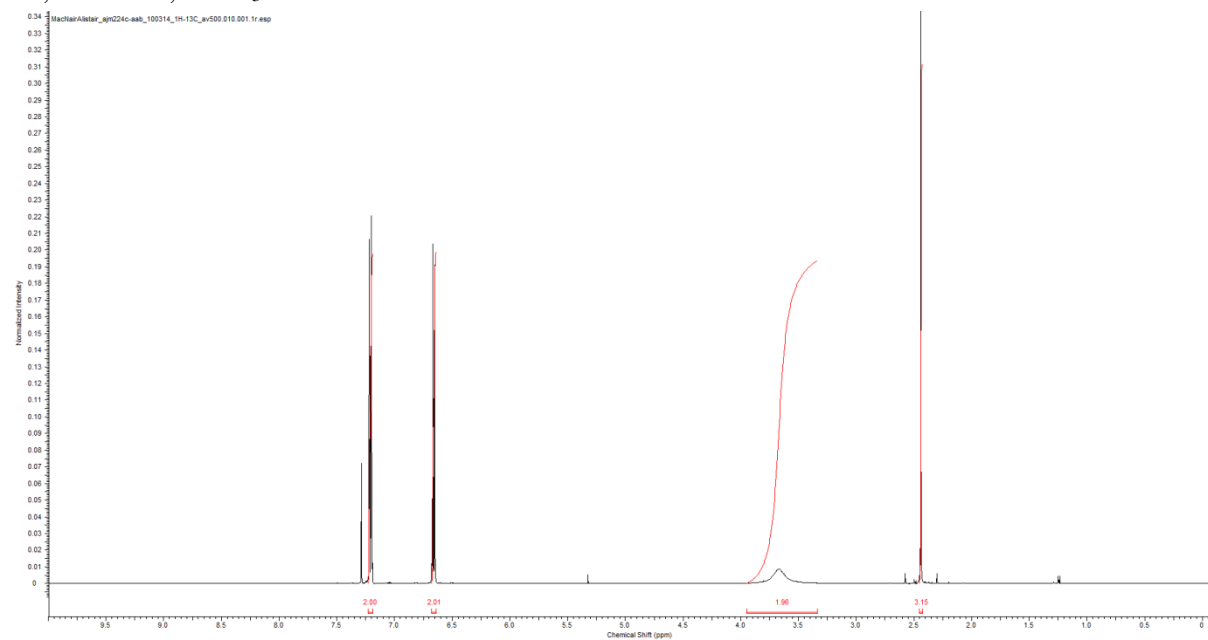
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



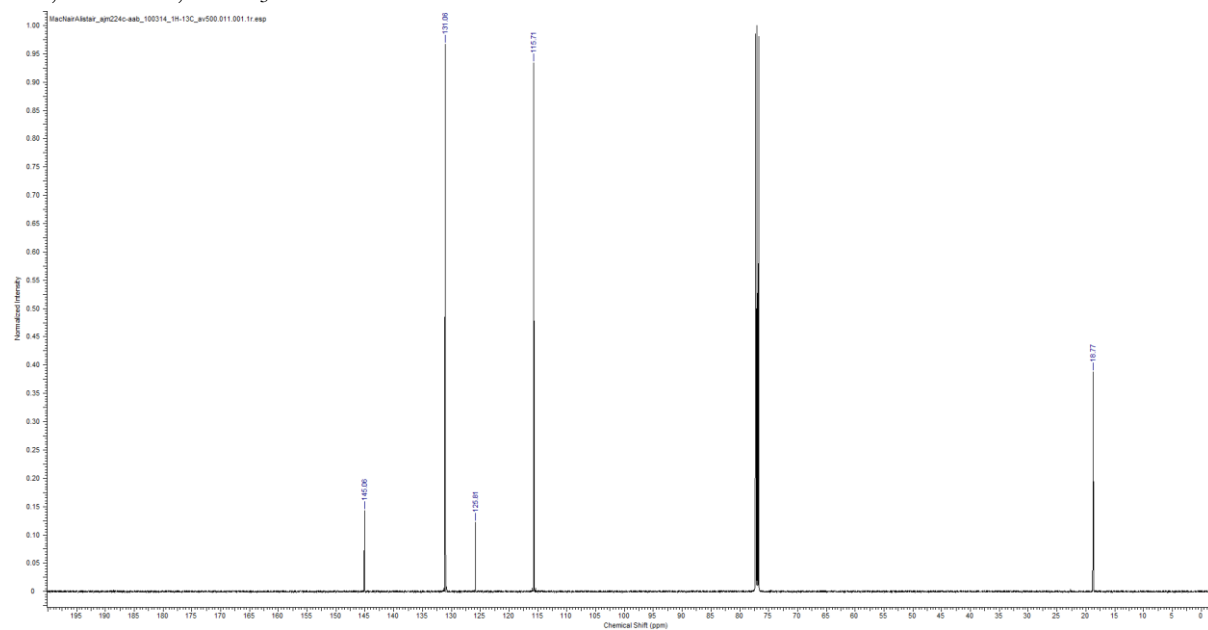
## 4-Methylsulfanylaniline (149)



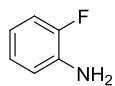
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



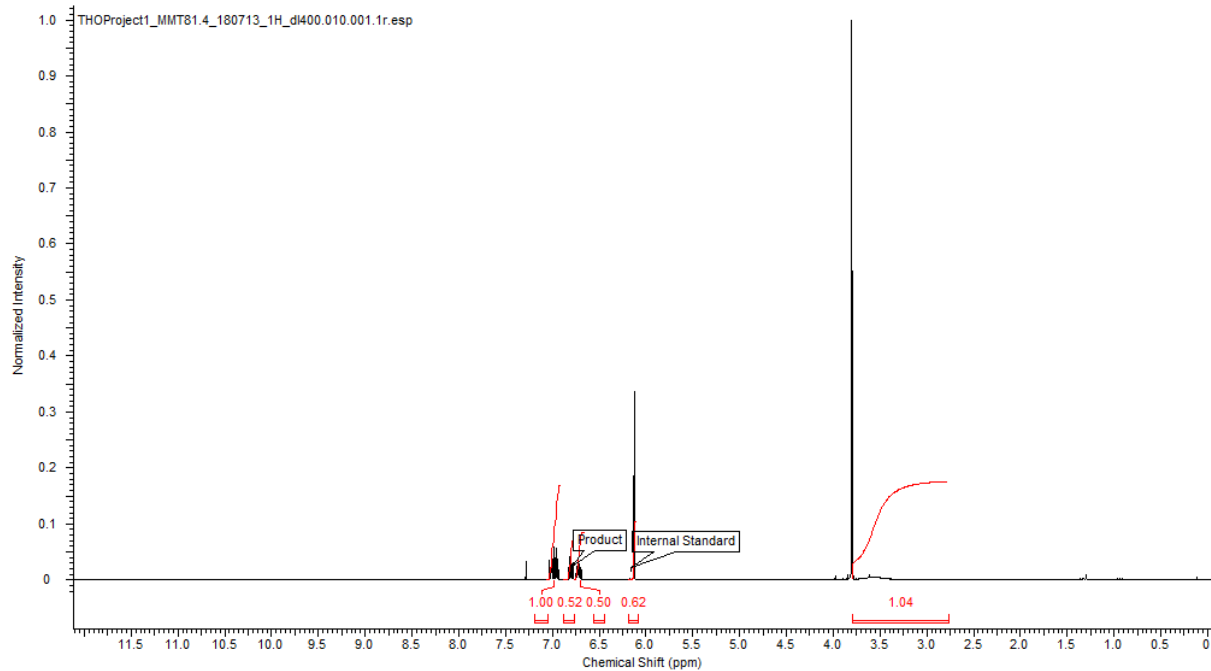
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



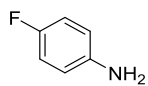
## 2-Fluoroaniline (151)



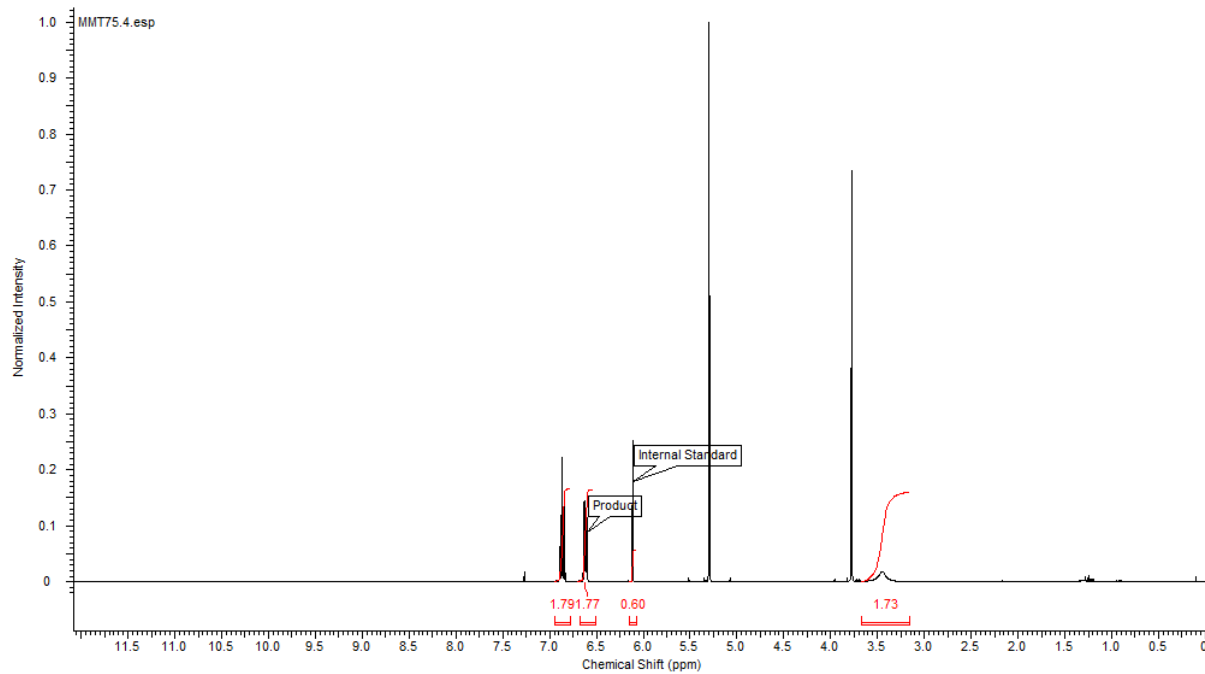
Crude reaction mixture:  $^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



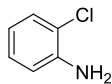
## 4-Fluoroaniline (152)



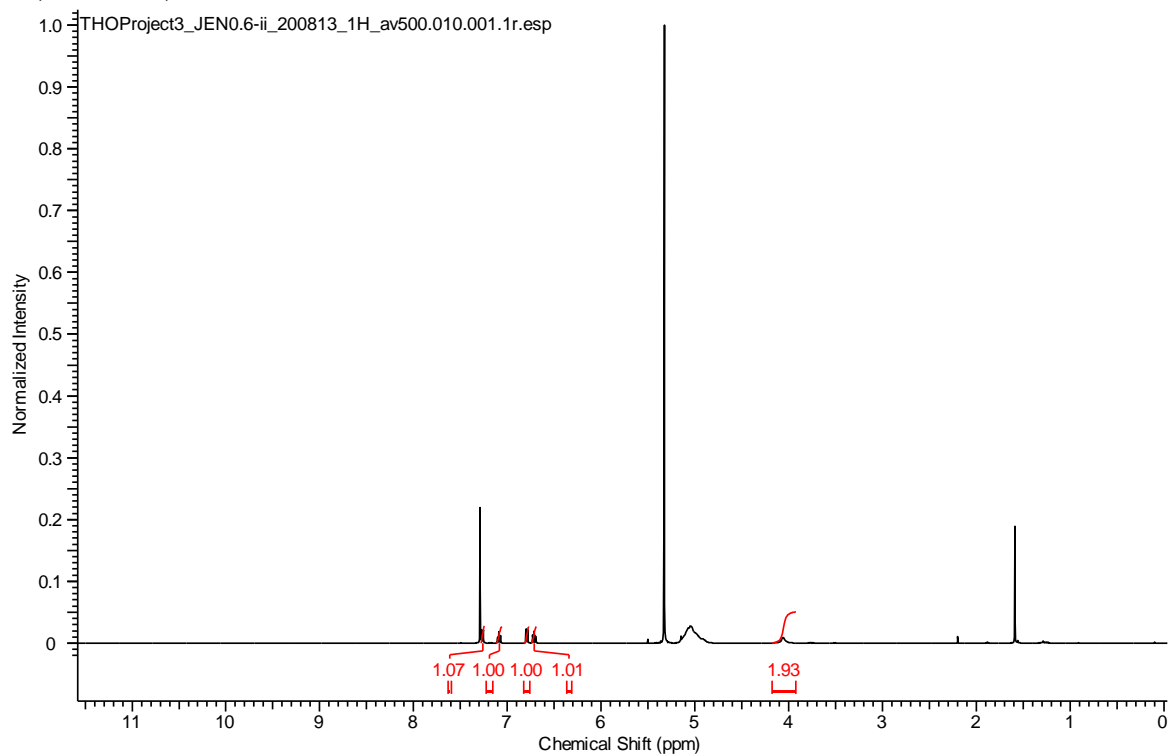
Crude reaction mixture:  $^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



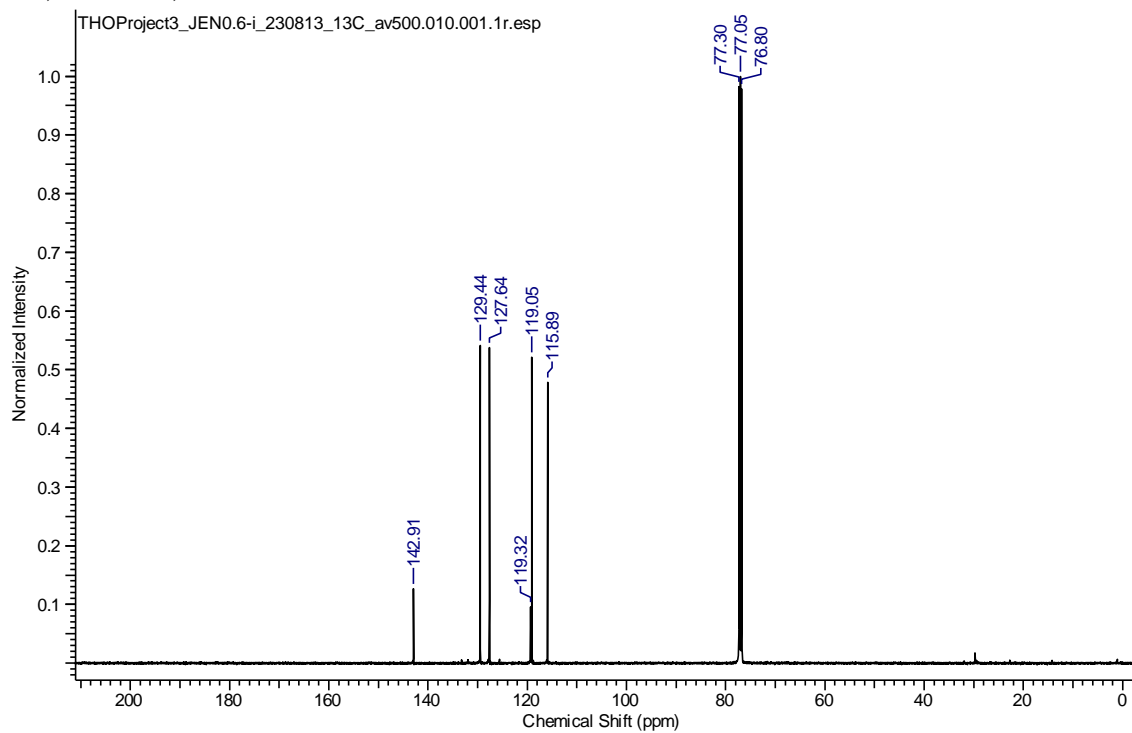
## 2-Chloroaniline (153)



$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$

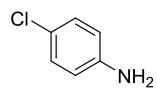


$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$

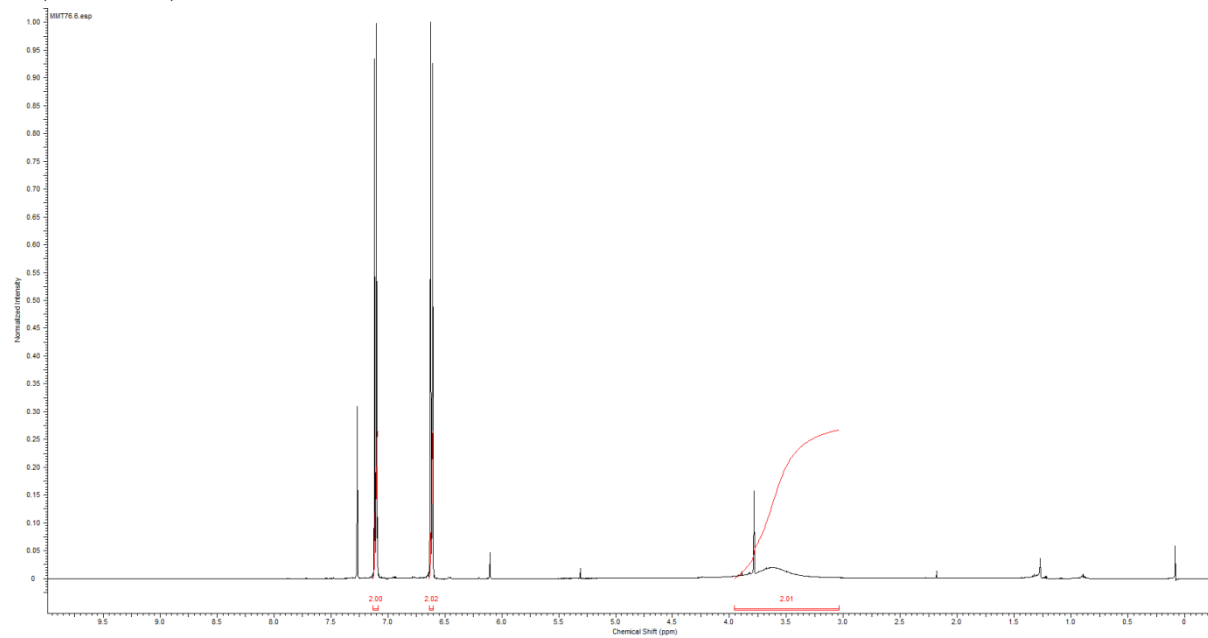




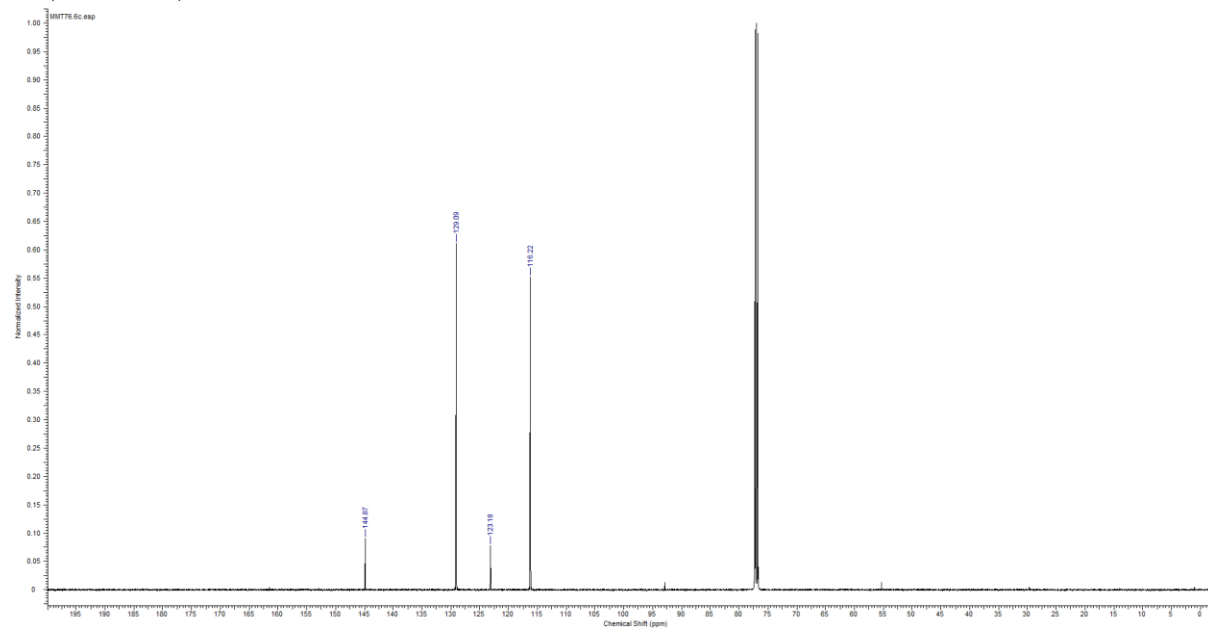
## 4-Chloroaniline (154)



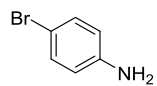
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



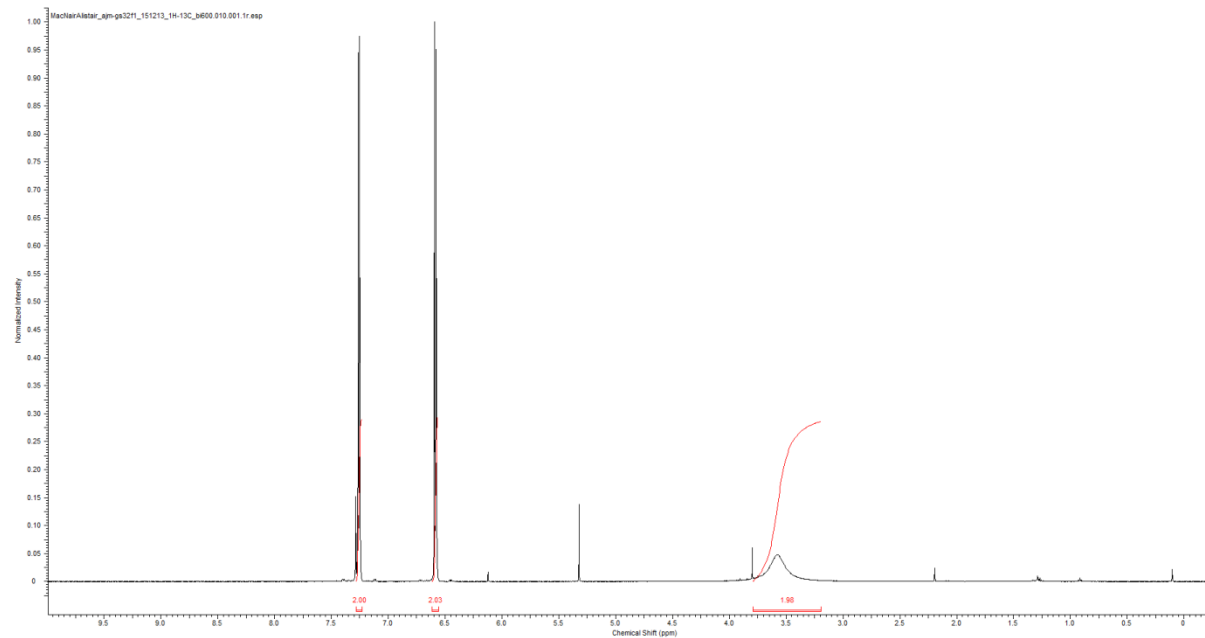
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



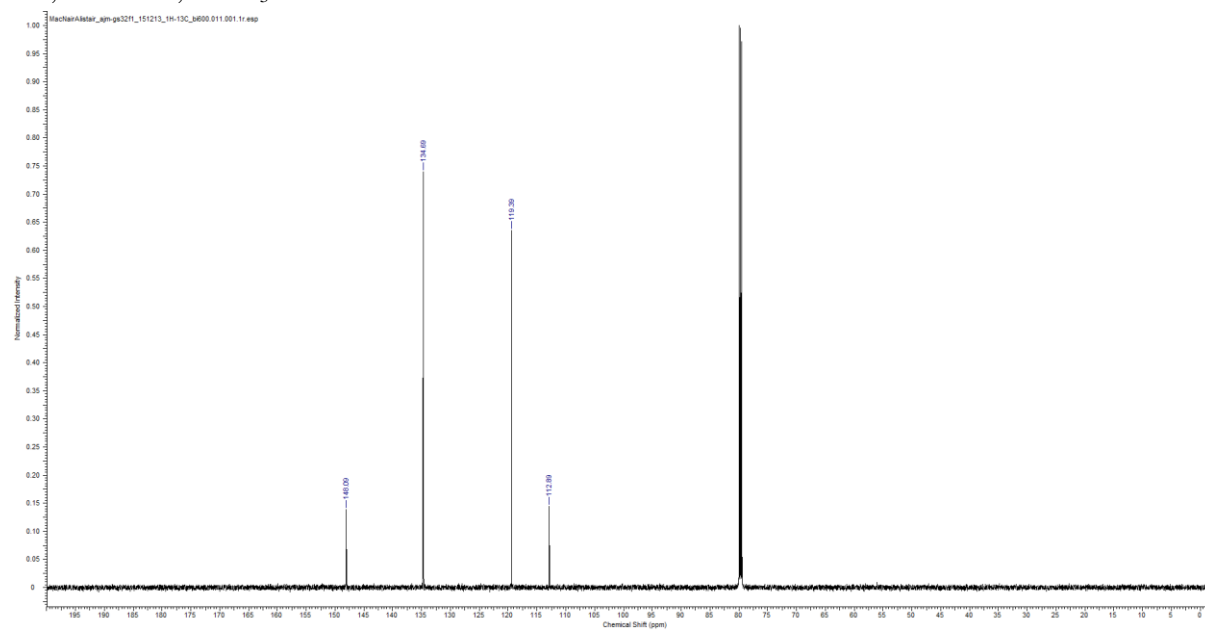
## 4-Bromoaniline (155)



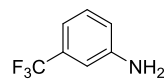
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



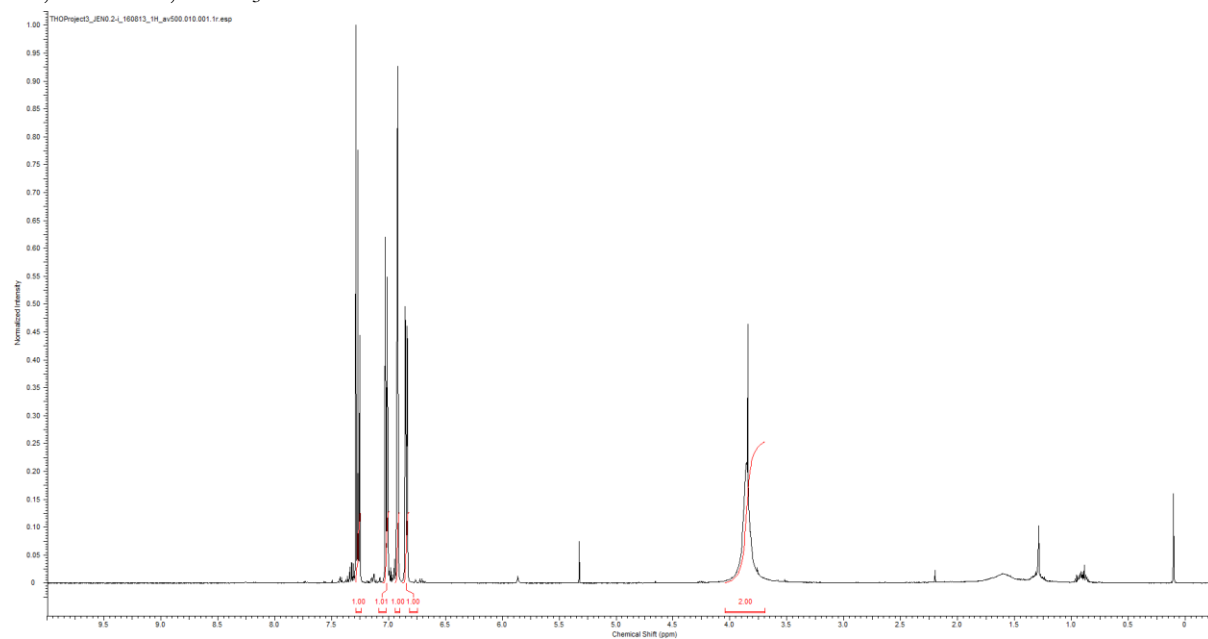
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



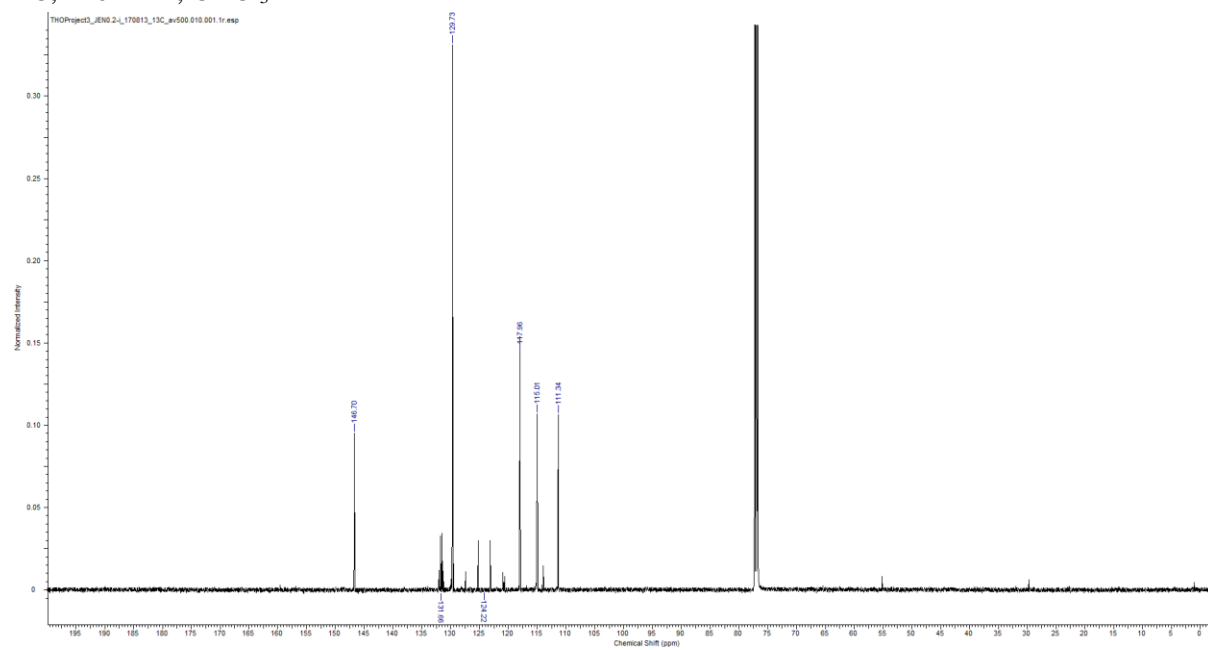
### 3-(Trifluoromethyl)aniline (156)



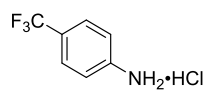
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



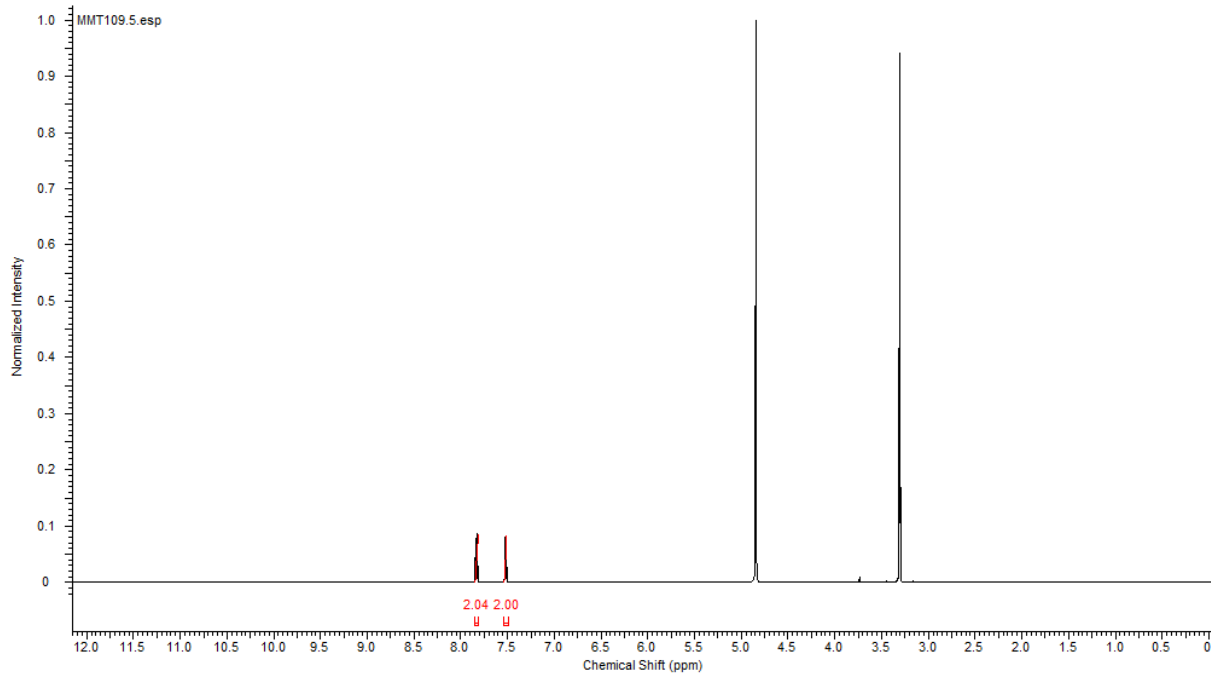
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



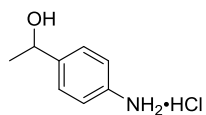
**4-(Trifluoromethyl)aniline hydrochloride (157)**



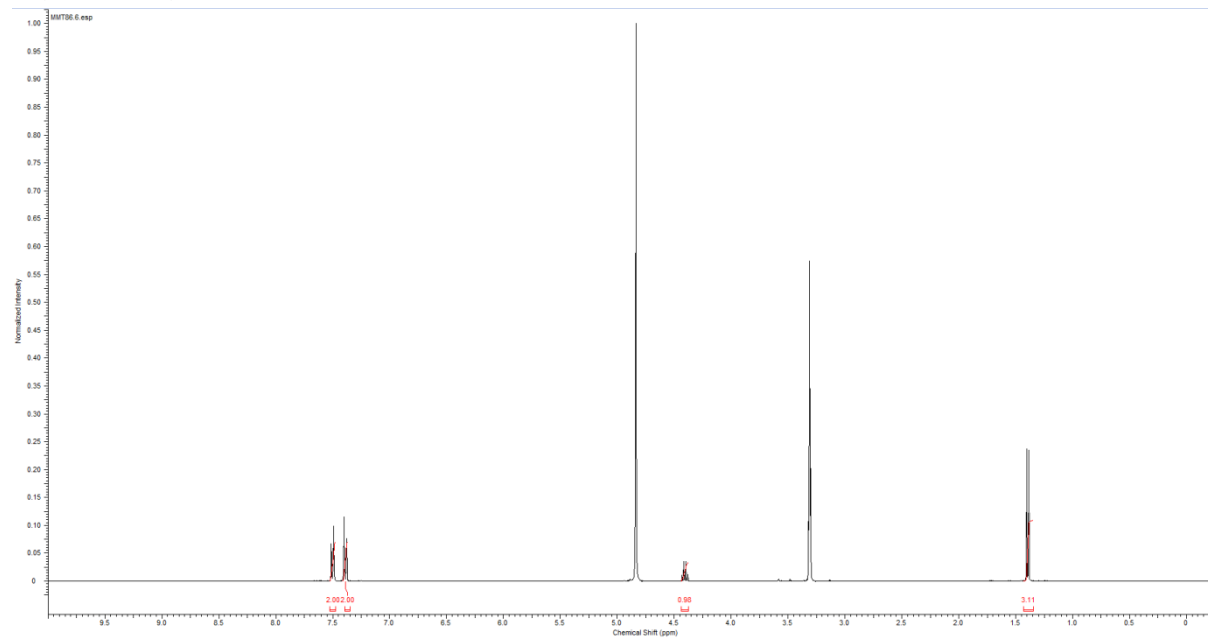
$^1\text{H}$ , 500 MHz,  $\text{CD}_3\text{OD}$



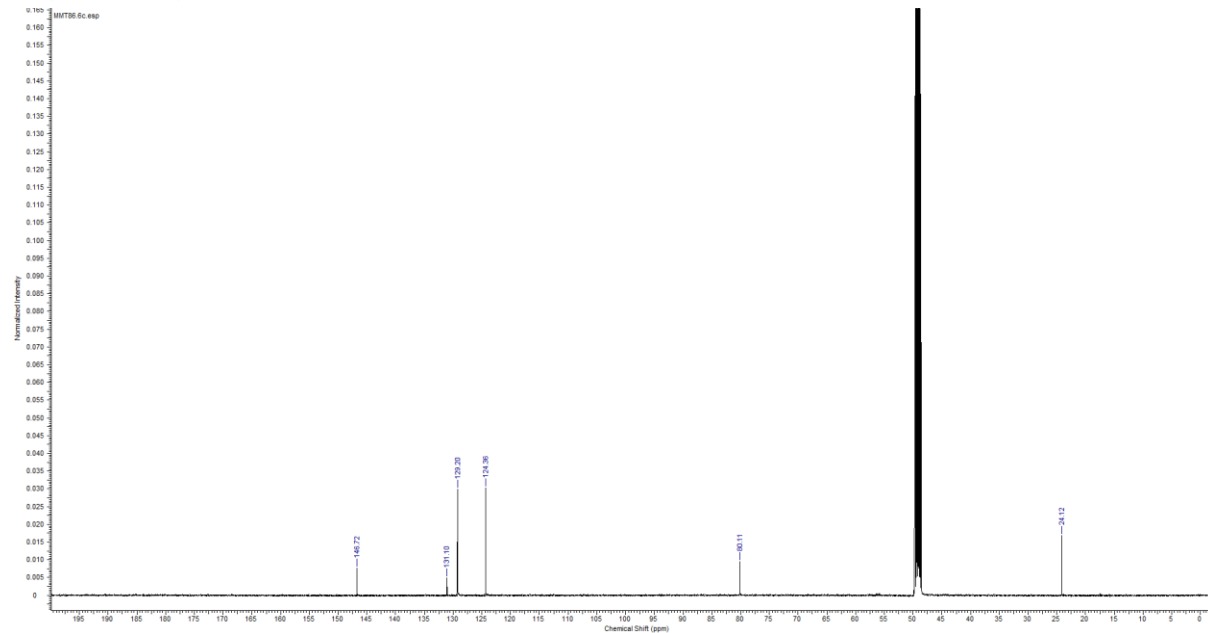
# 1-(4-Aminophenyl)ethanol hydrochloride (158)



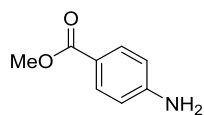
$^1\text{H}$ , 400 MHz,  $\text{CD}_3\text{OD}$



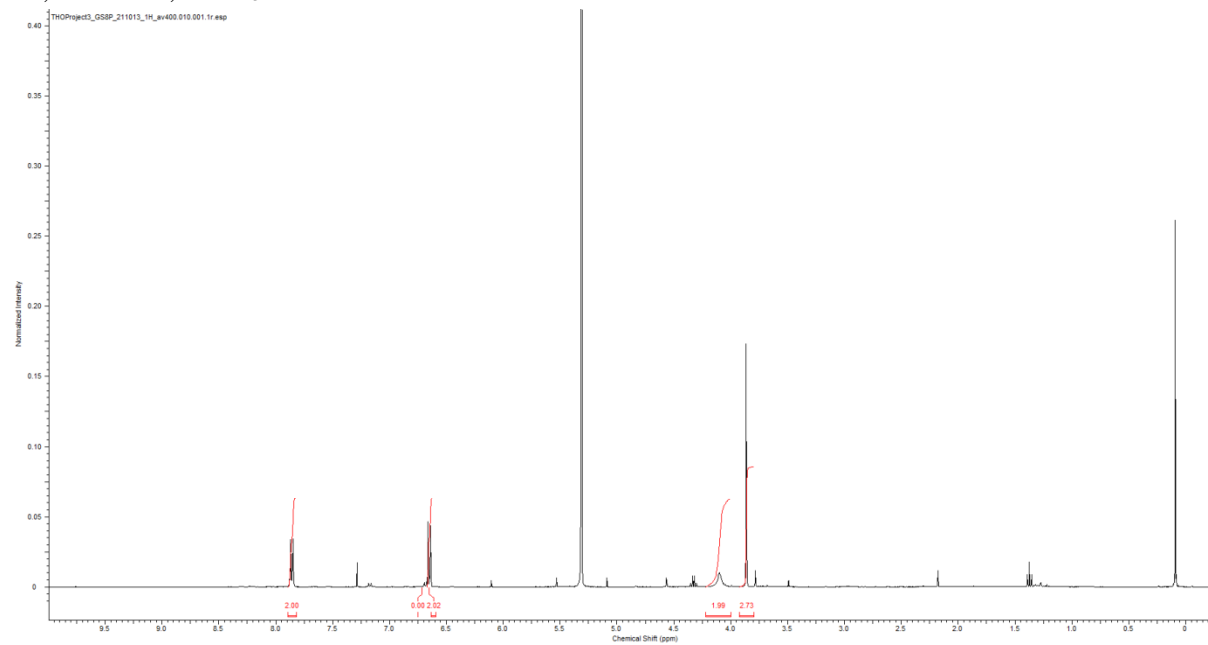
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_3\text{OD}$



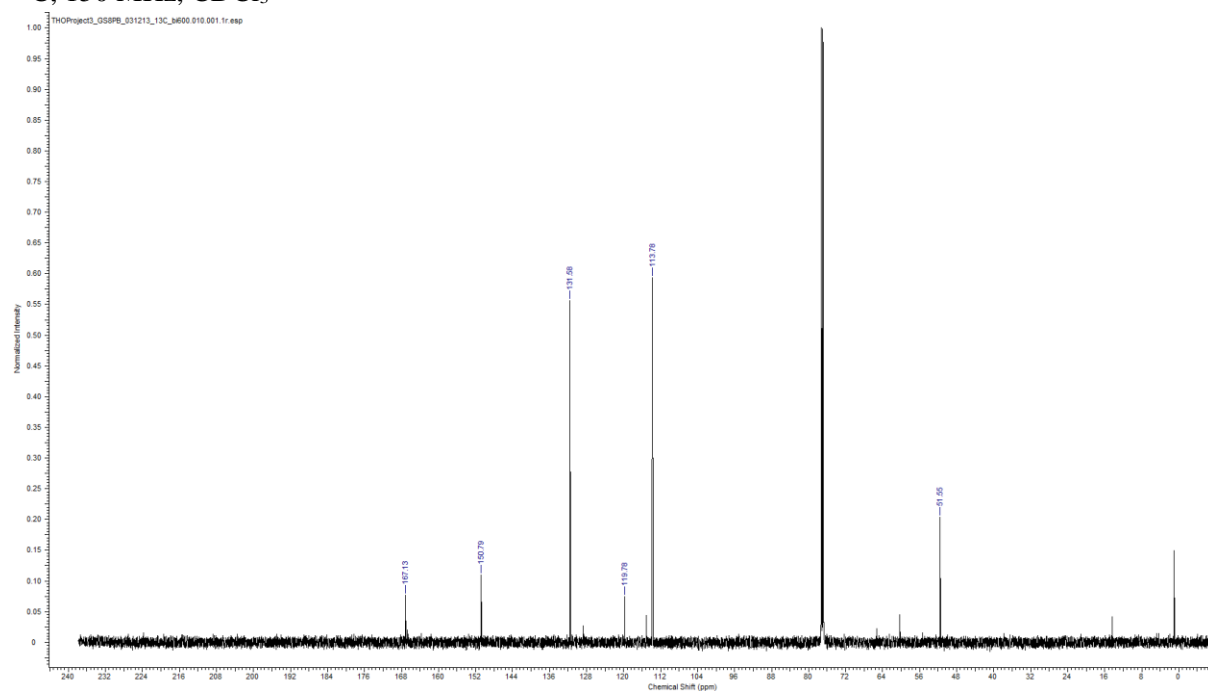
## Methyl 4-aminobenzoate (159)



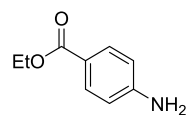
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



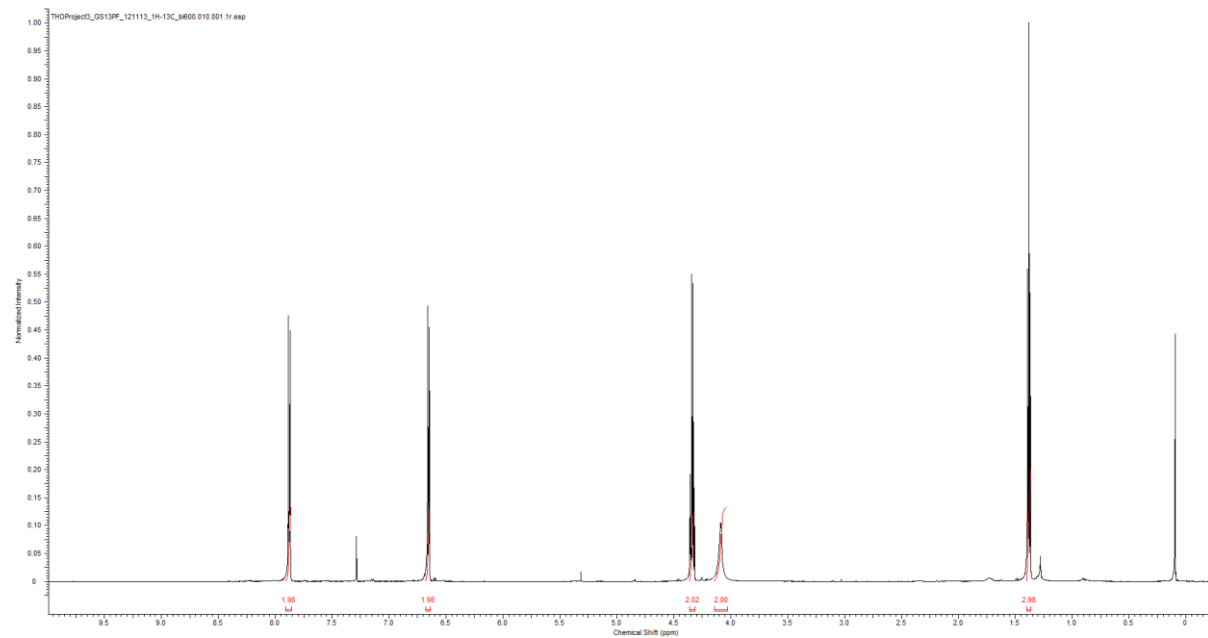
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



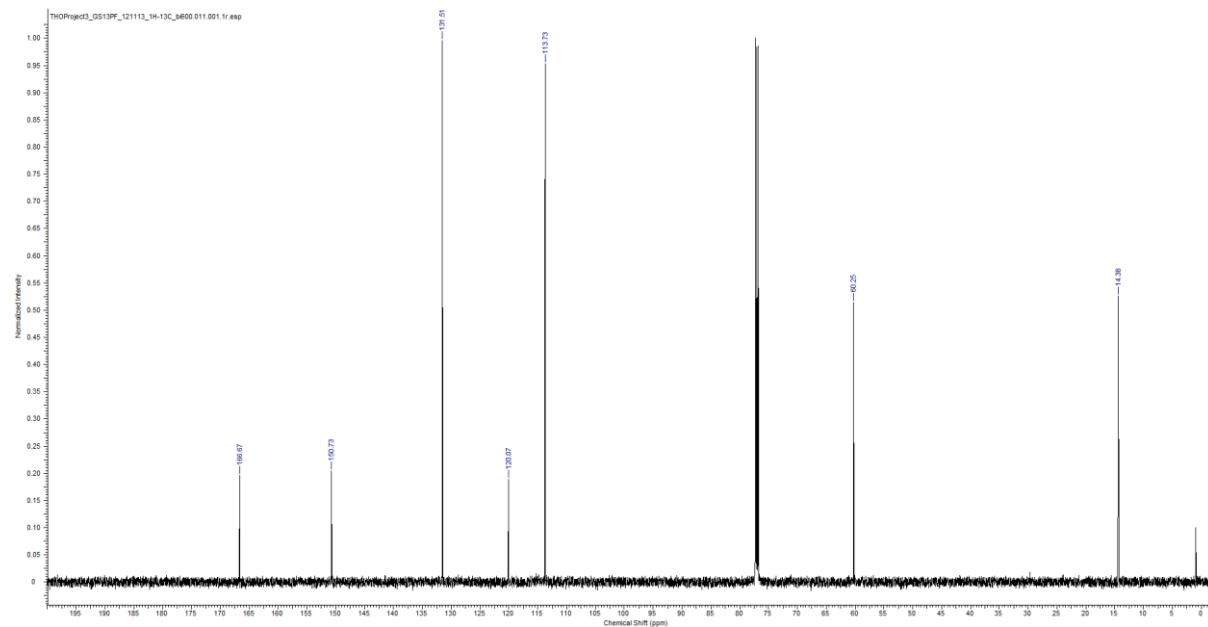
## Ethyl 4-aminobenzoate (160)



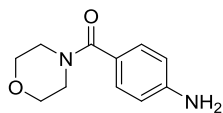
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



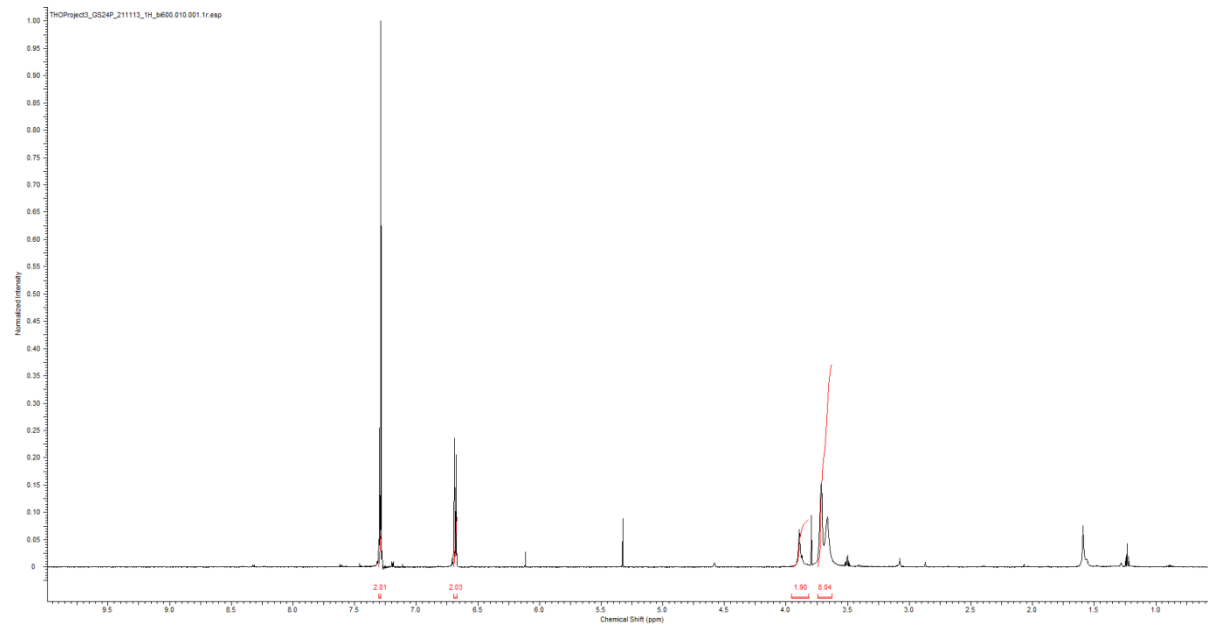
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



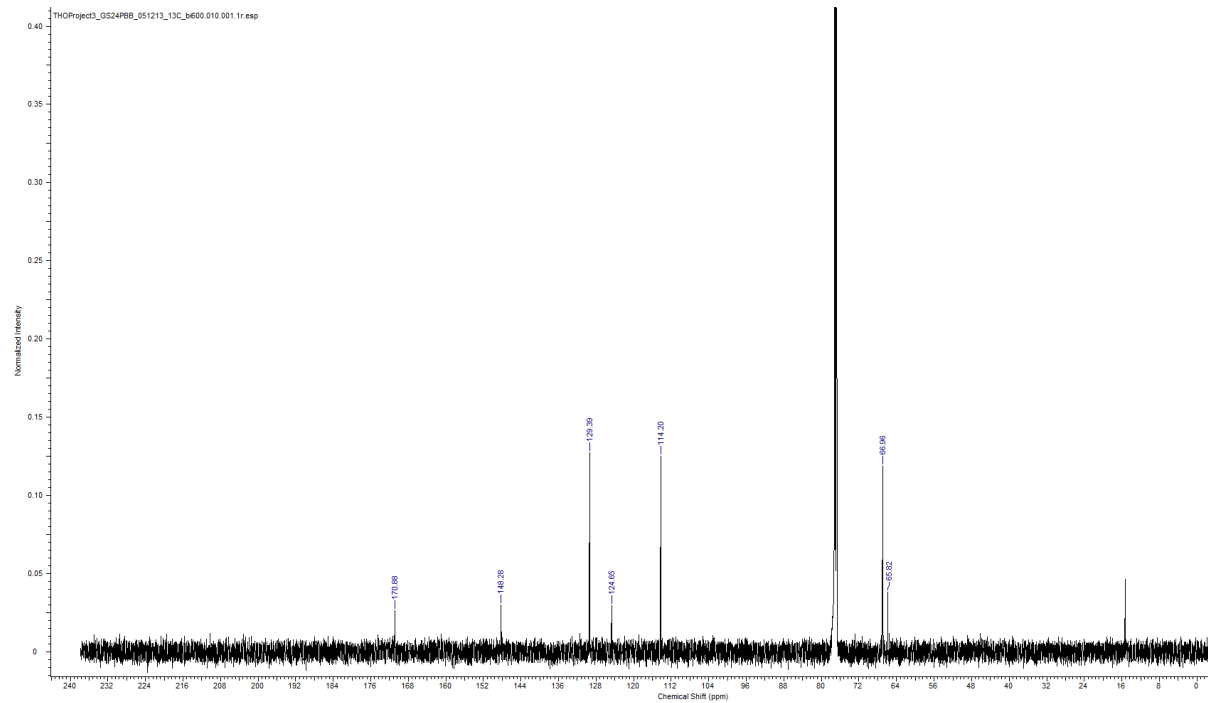
## 4-(4-Aminobenzoyl)morpholine (161)



$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$

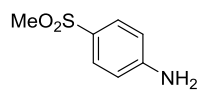


$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$

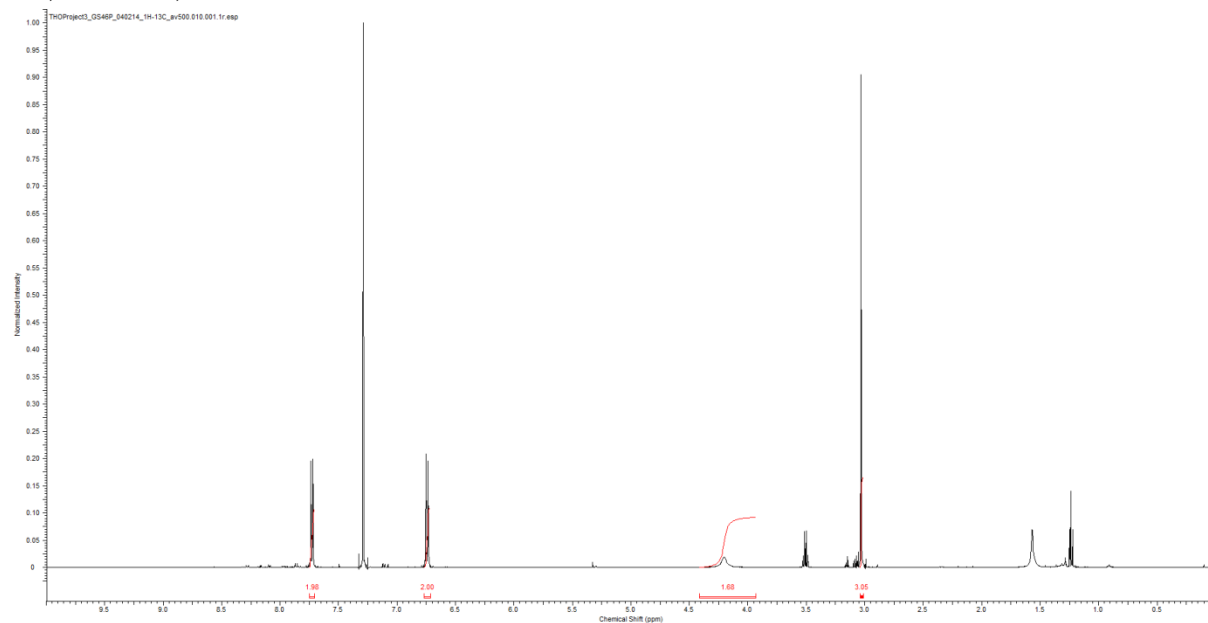




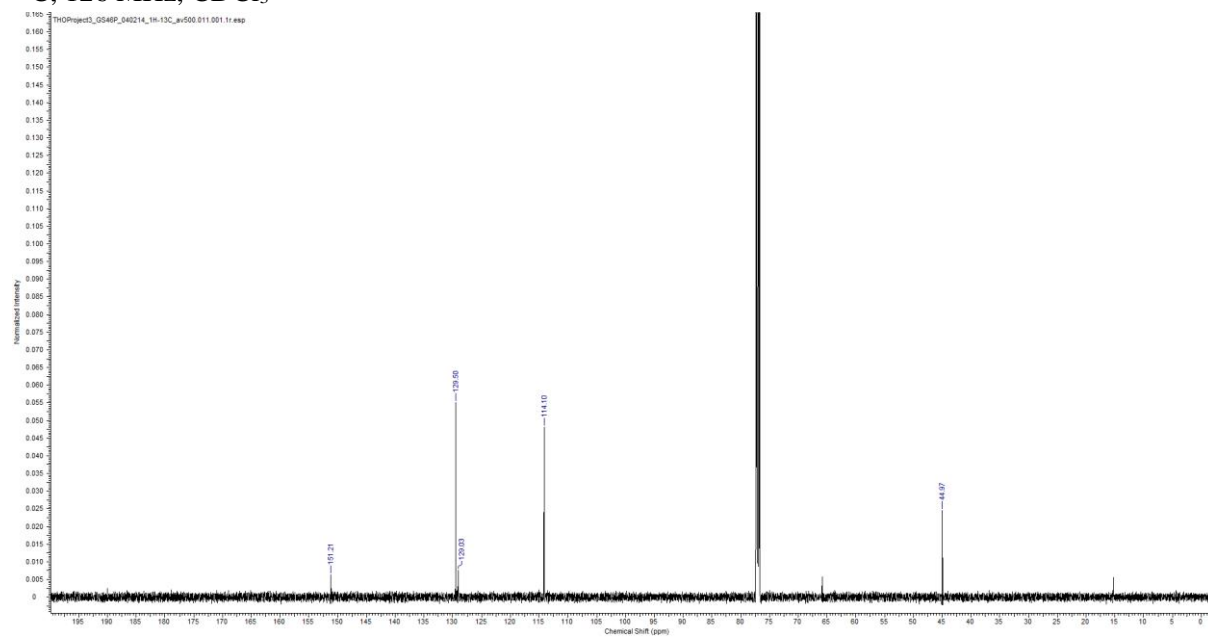
## 4-(Methylsulfonyl)-aniline (162)



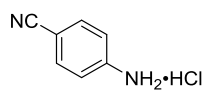
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



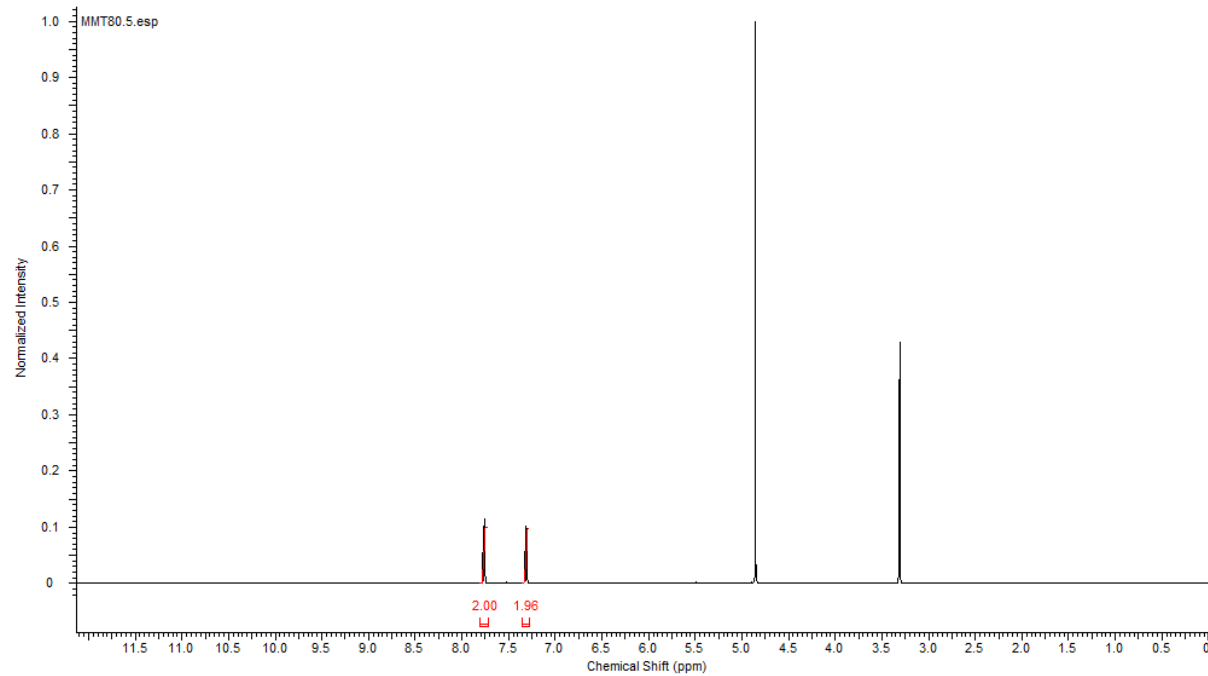
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



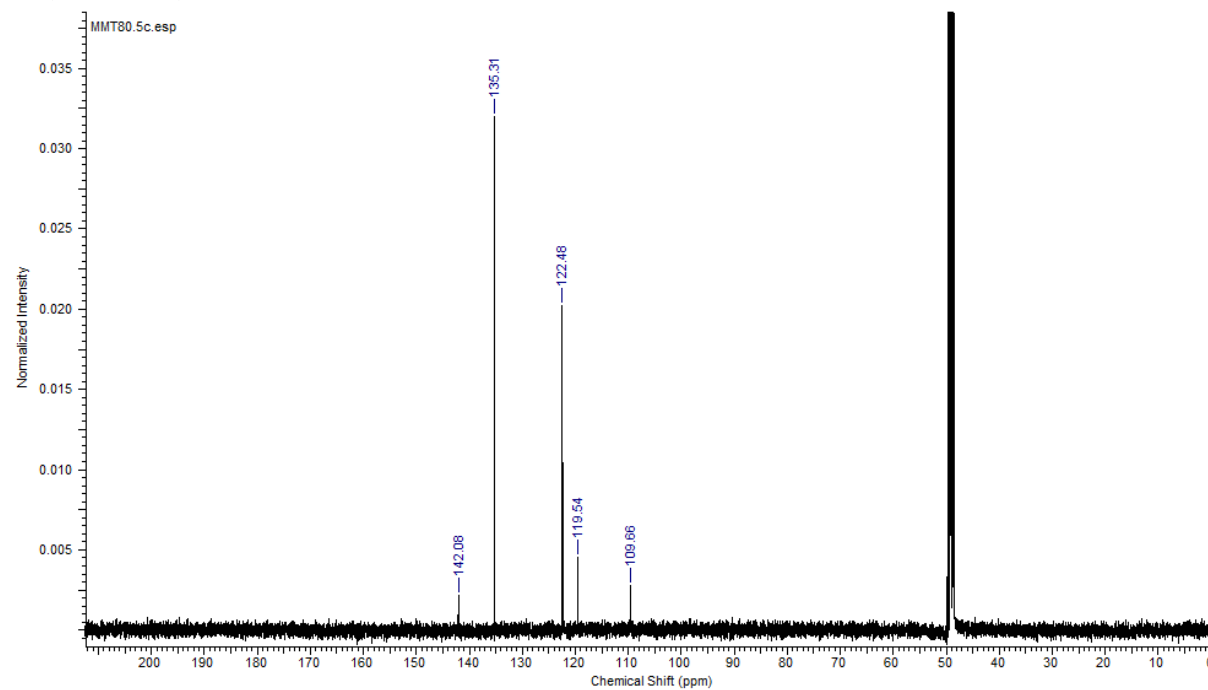
# 4-Aminobenzonitrile hydrochloride (163)



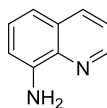
$^1\text{H}$ , 600 MHz,  $\text{CD}_3\text{OD}$



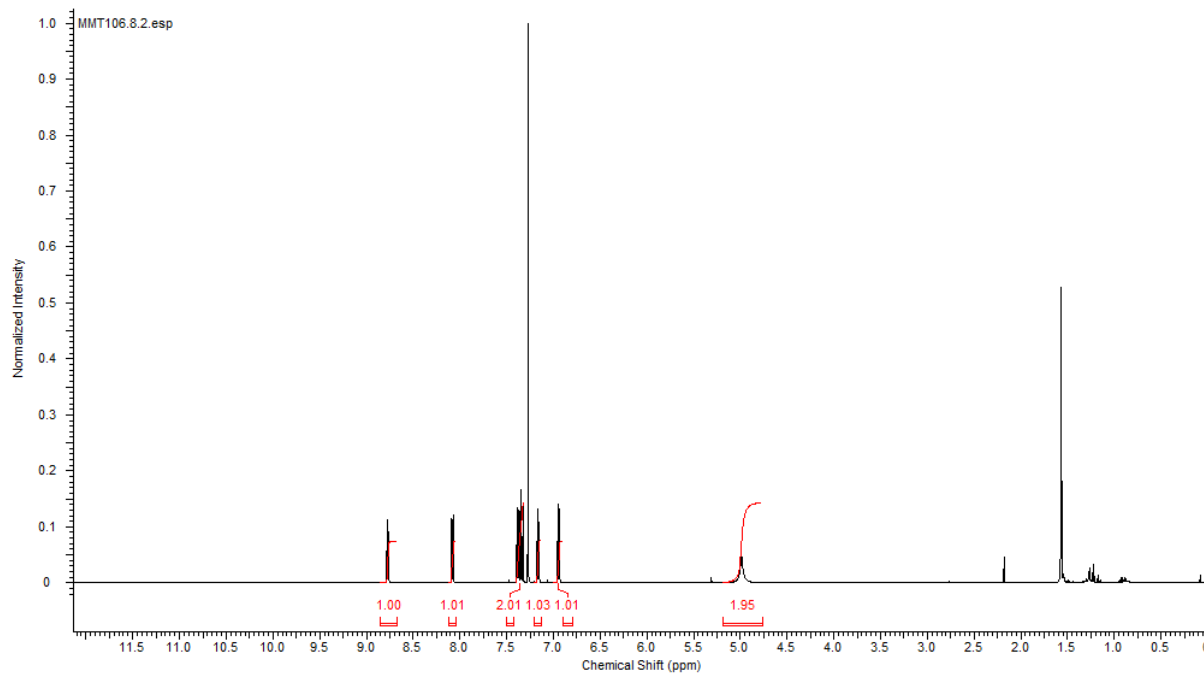
$^{13}\text{C}$ , 150 MHz,  $\text{CD}_3\text{OD}$



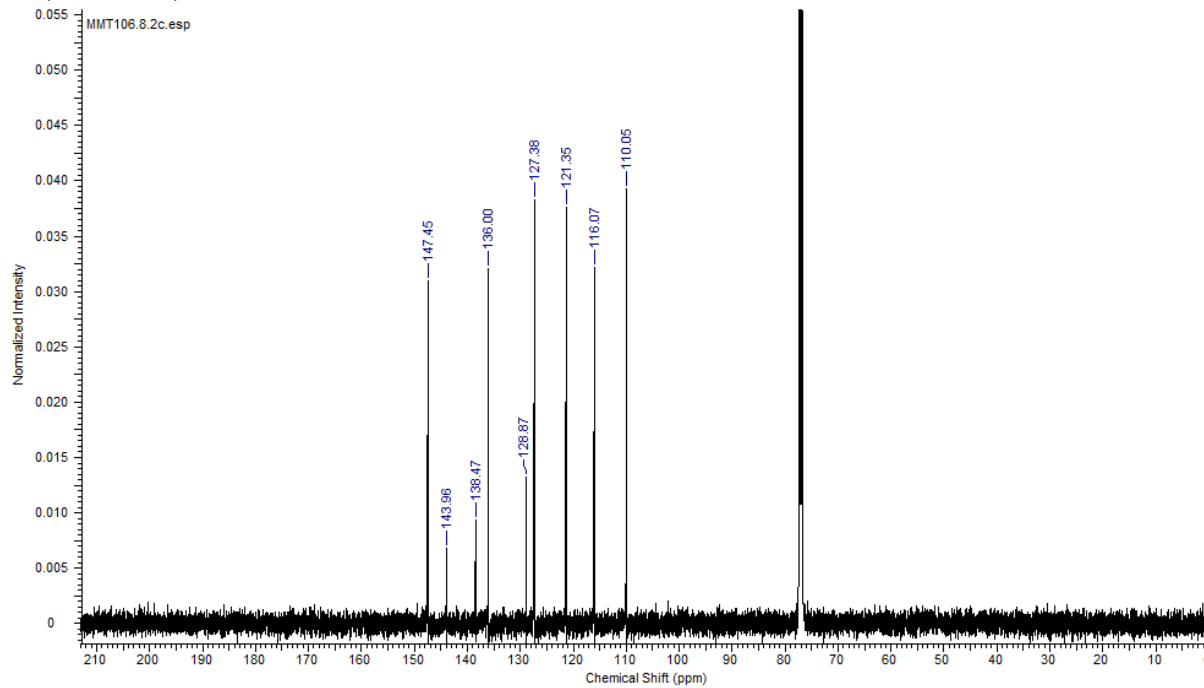
## 8-Aminoquinoline (164)



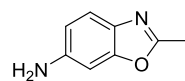
$^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



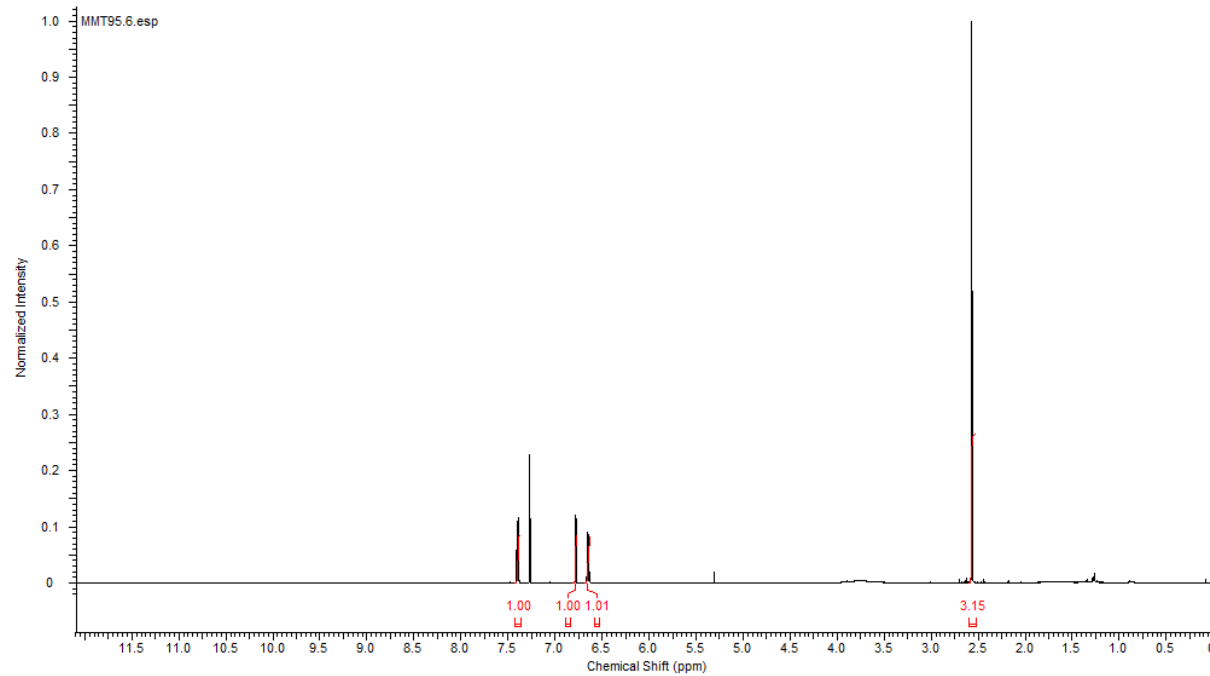
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



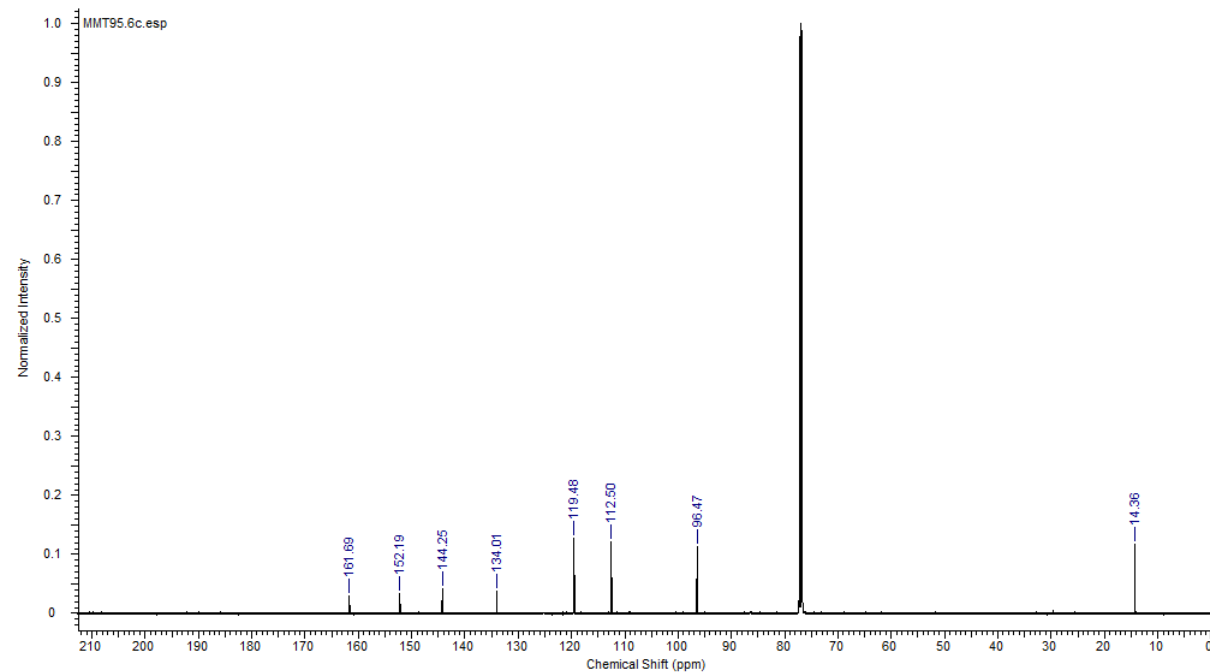
## 2-Methyl-6-benzoxazolamine (165)



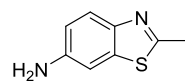
$^1\text{H}$ , 400 MHz,  $\text{CDCl}_3$



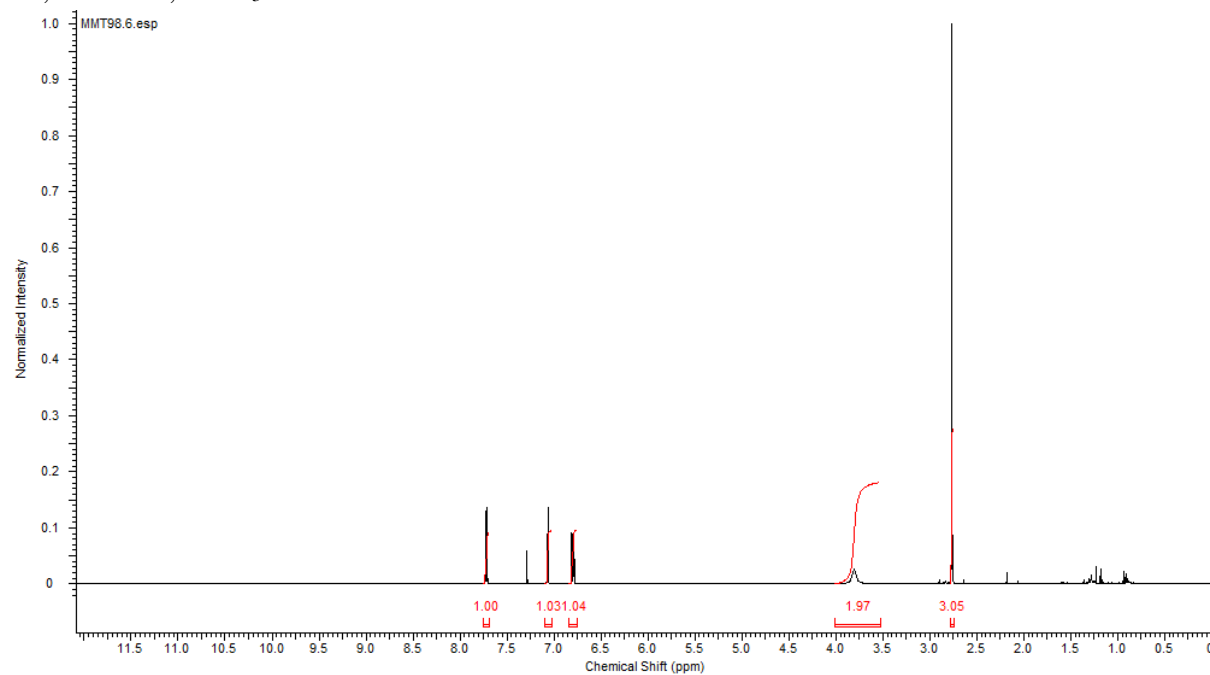
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



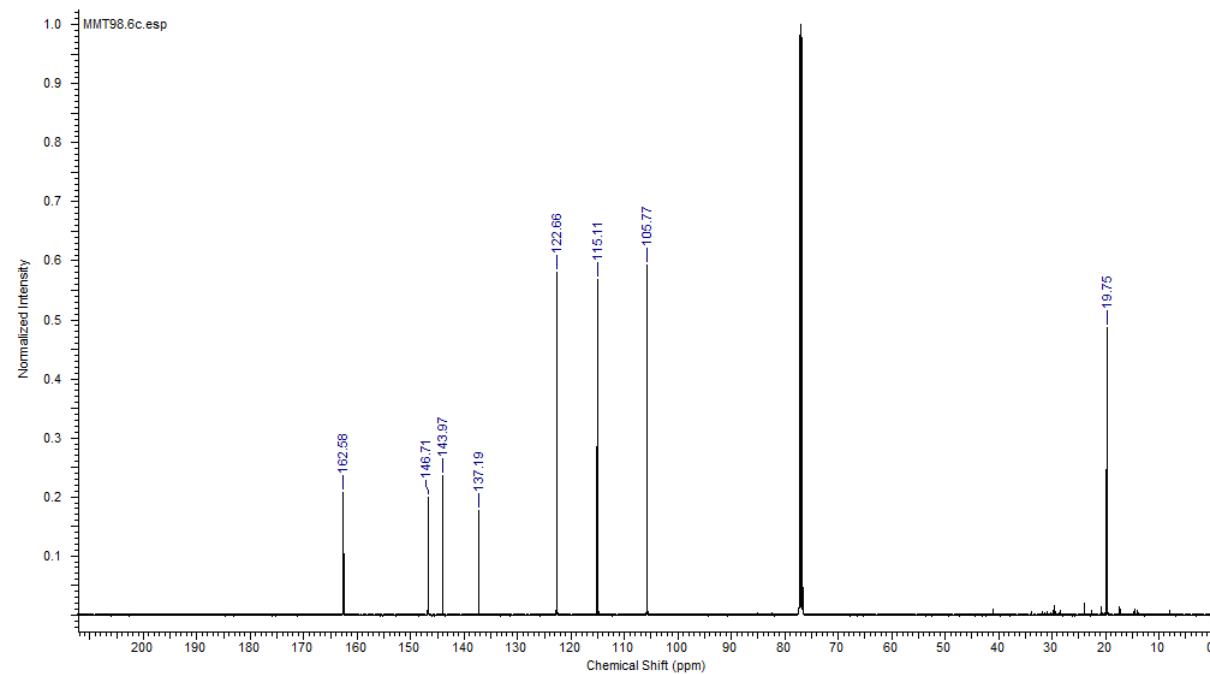
## 2-Methyl-6-benzothiazolamine (166)



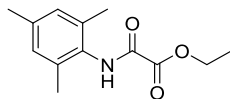
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



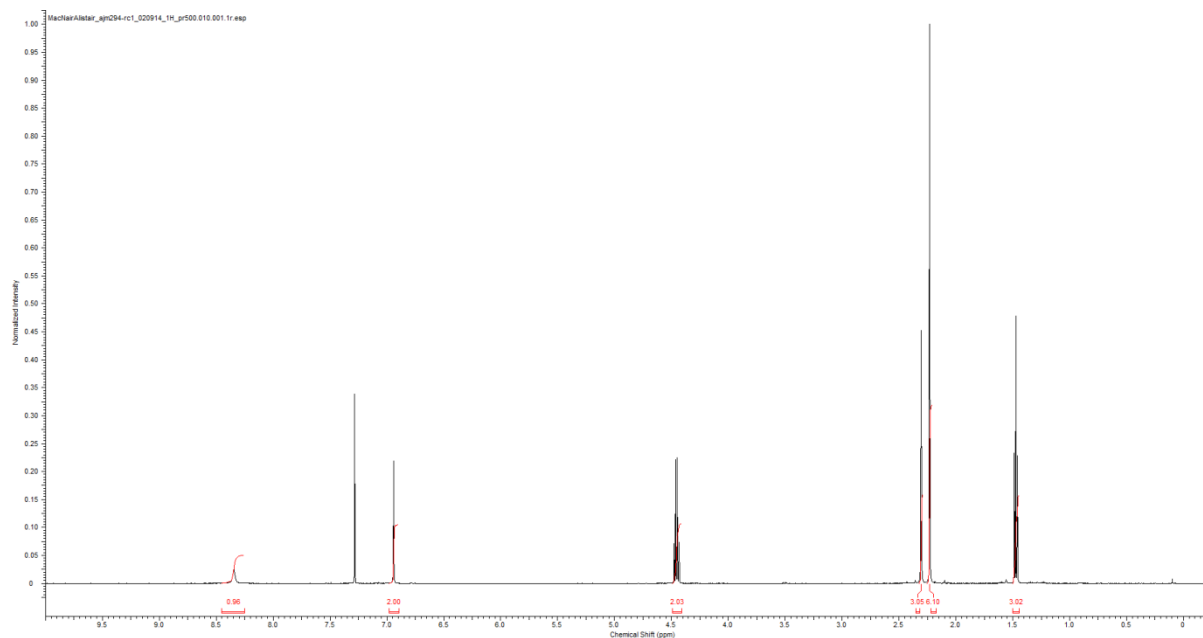
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



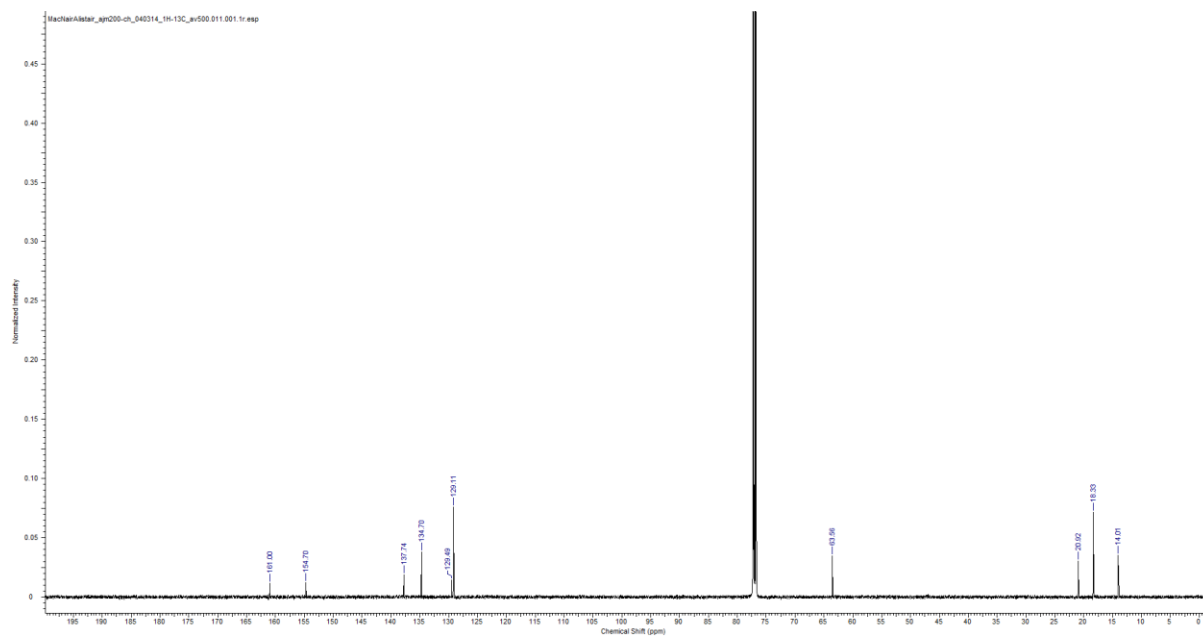
***N*-(2,4,6-Trimethylphenyl)-oxalamic acid, ethyl ester (231)**



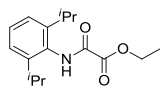
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



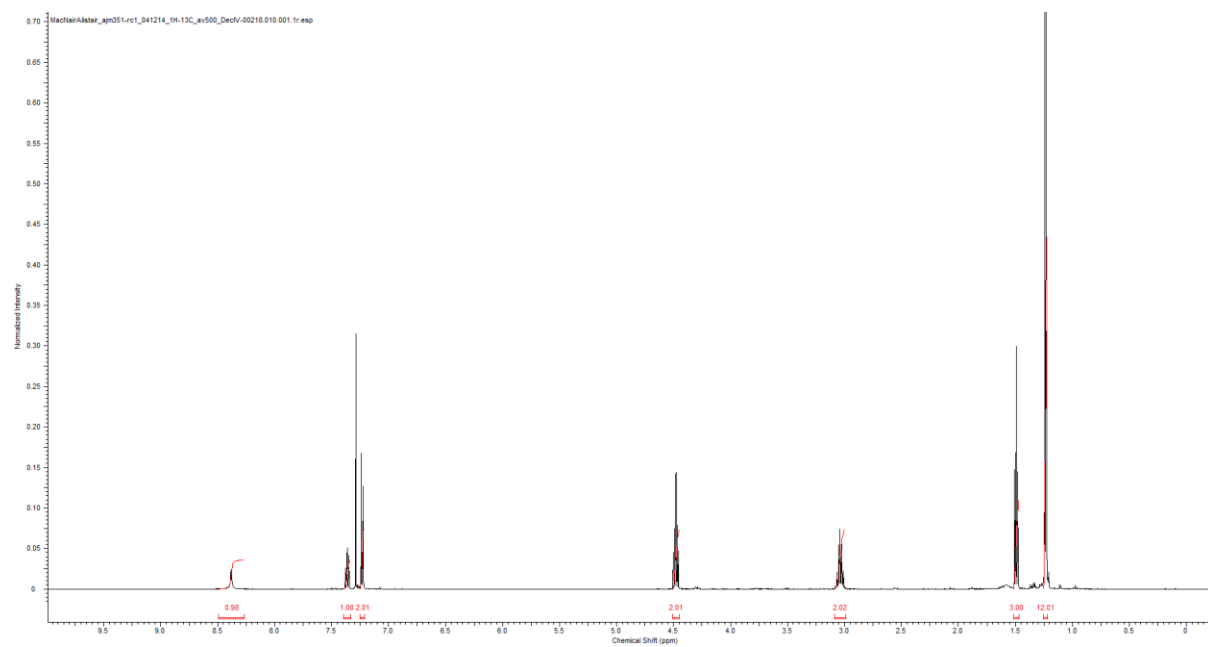
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



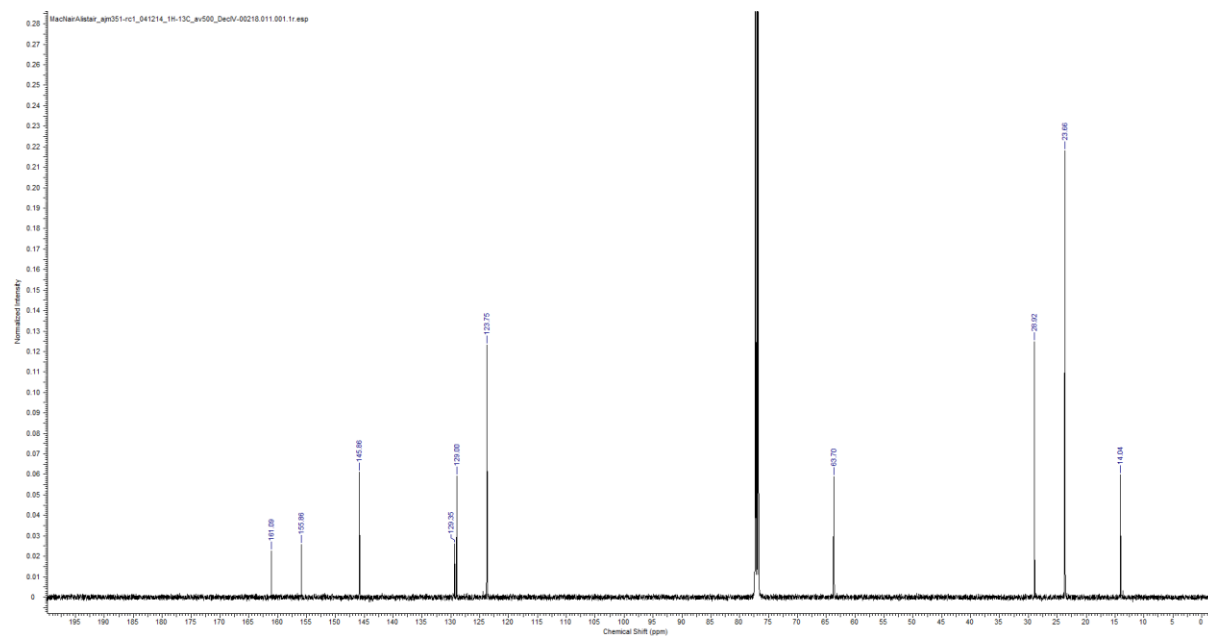
## Oxanilic acid, 2', 6'-diisopropyl-, ethyl ester (232)



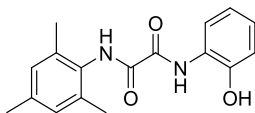
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



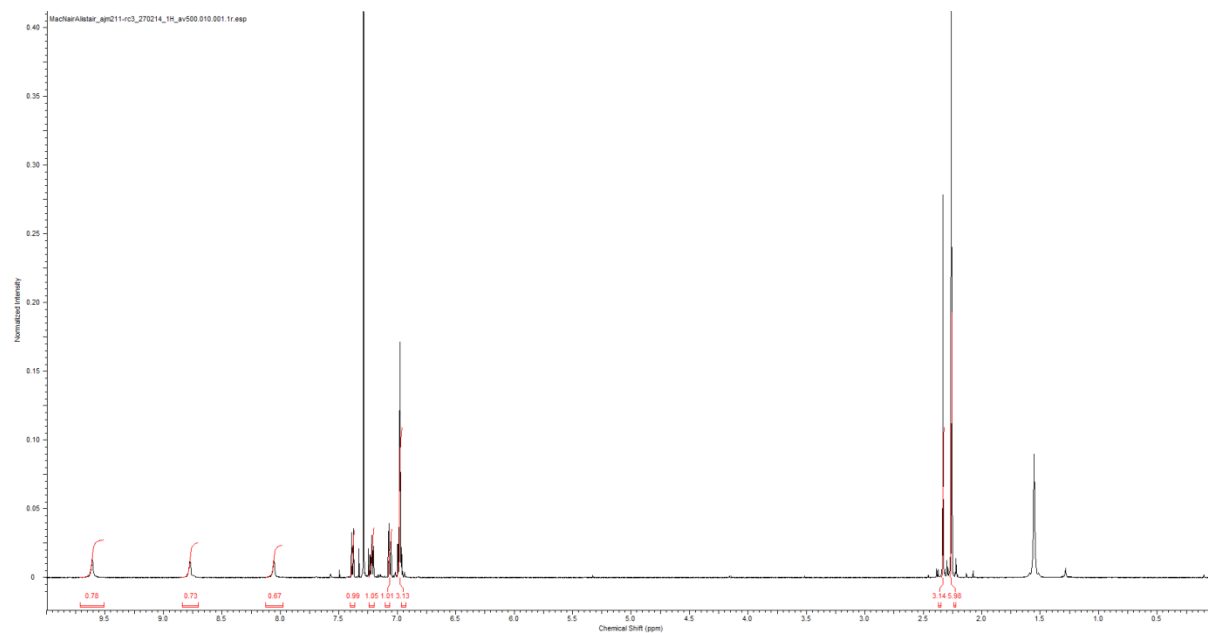
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



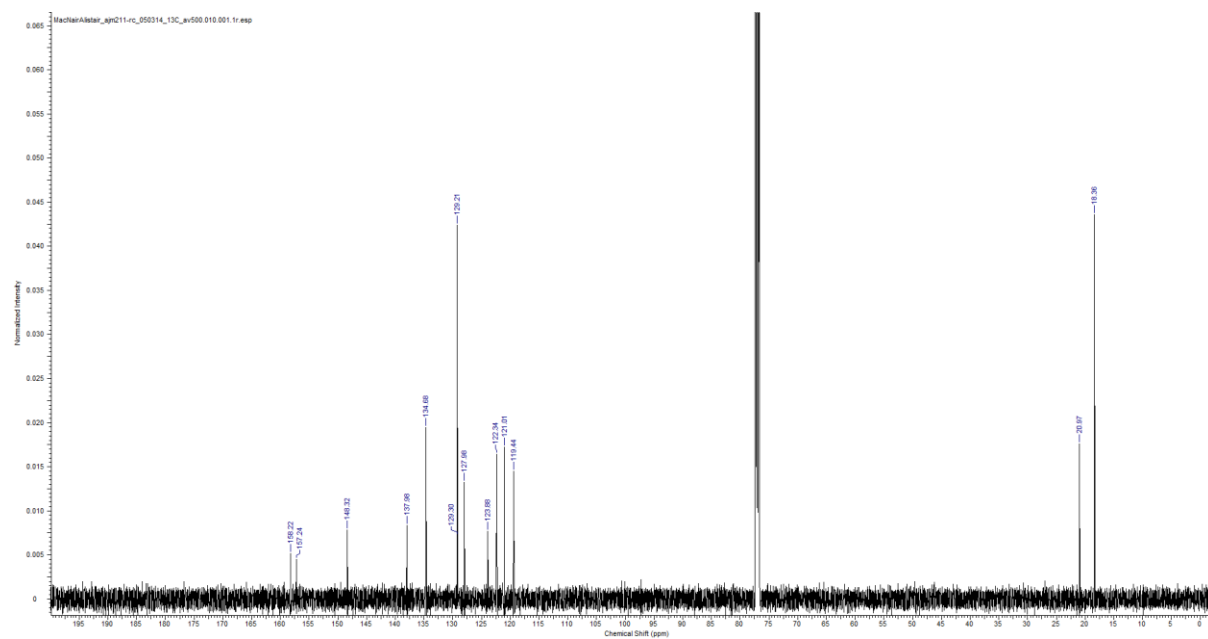
**Ethanediamide, N-(2-hydroxyphenyl)-N'-(2,4,6-trimethylphenyl)- (233)**



$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$

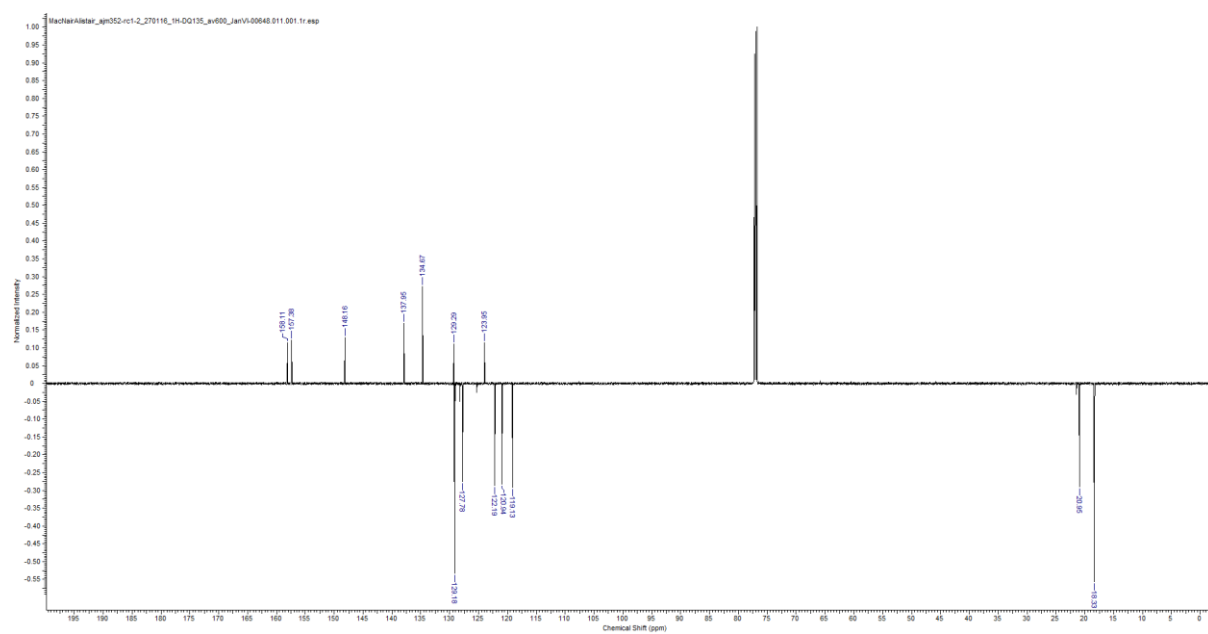


$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$

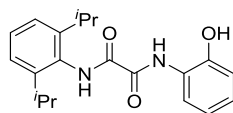




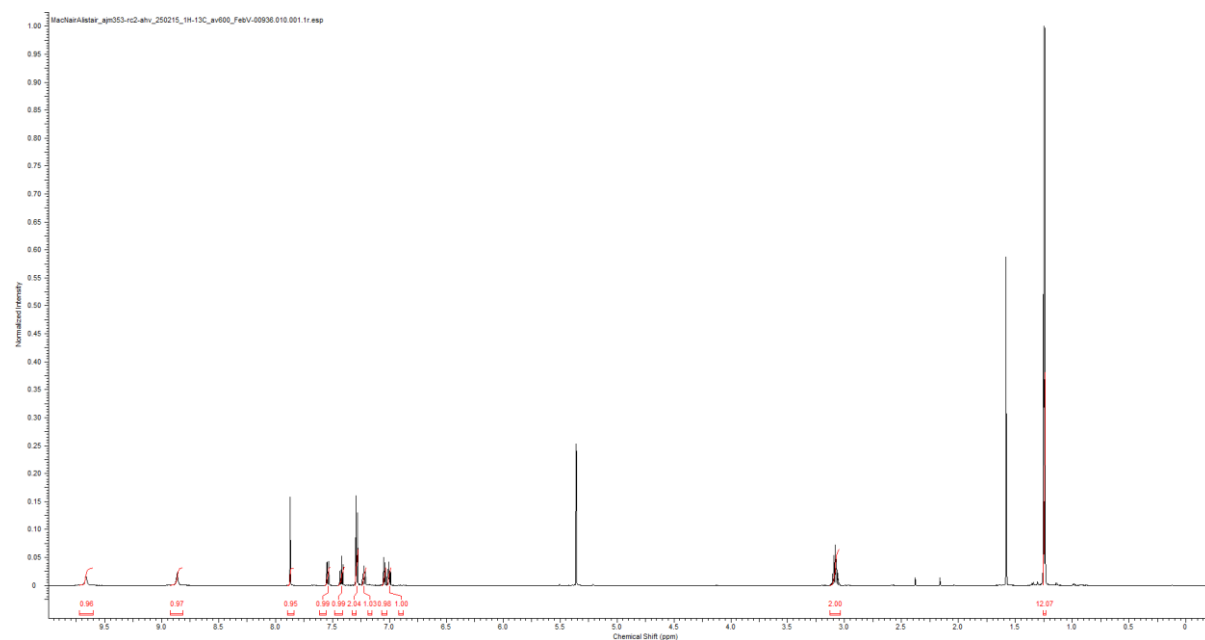
$^{13}\text{C}$  DEPT (with quaternary), 150 MHz,  $\text{CDCl}_3$



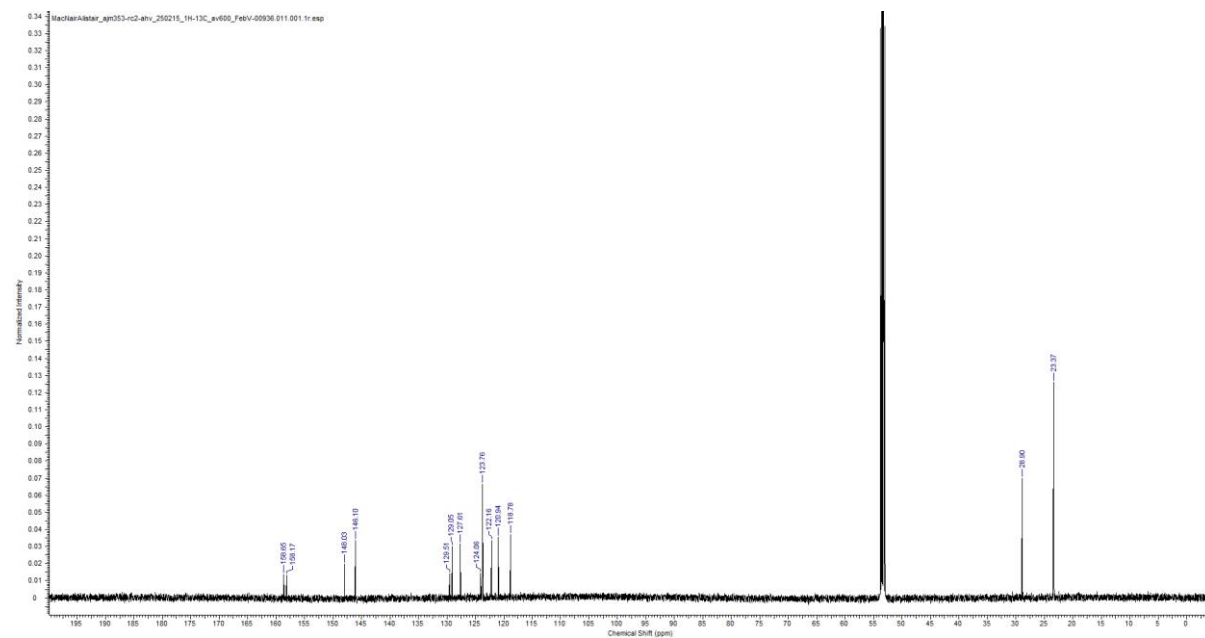
## Ethanediamide, N-(2-hydroxyphenyl)-N'-(2,6-diisopropylphenyl) (234)



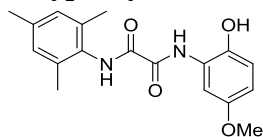
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



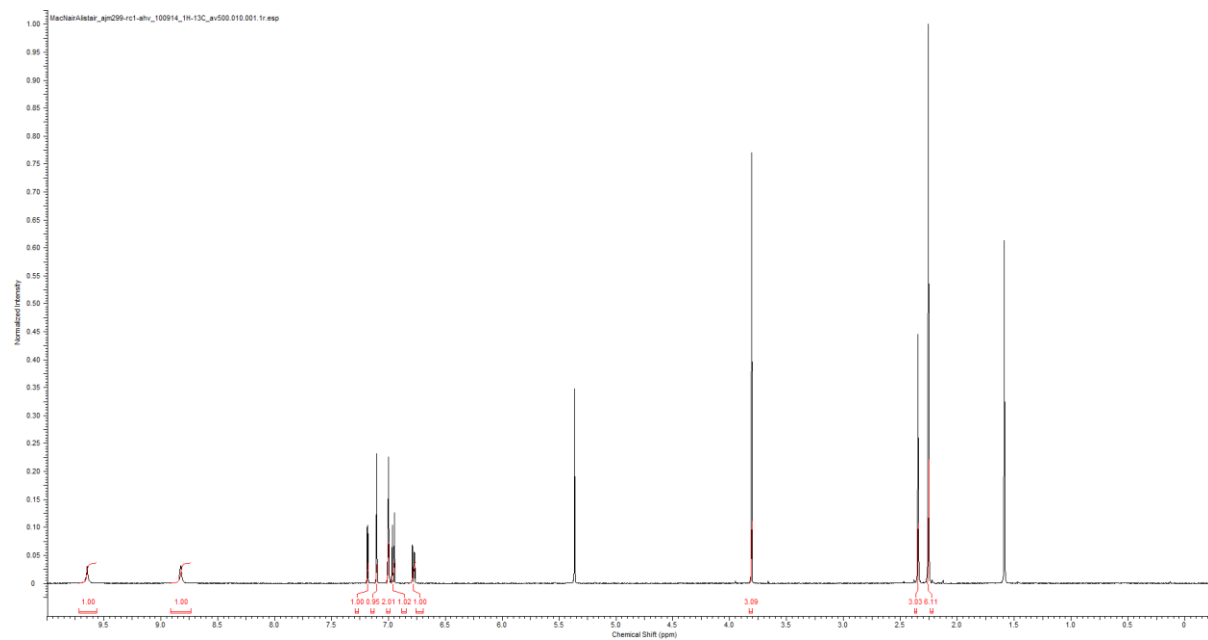
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



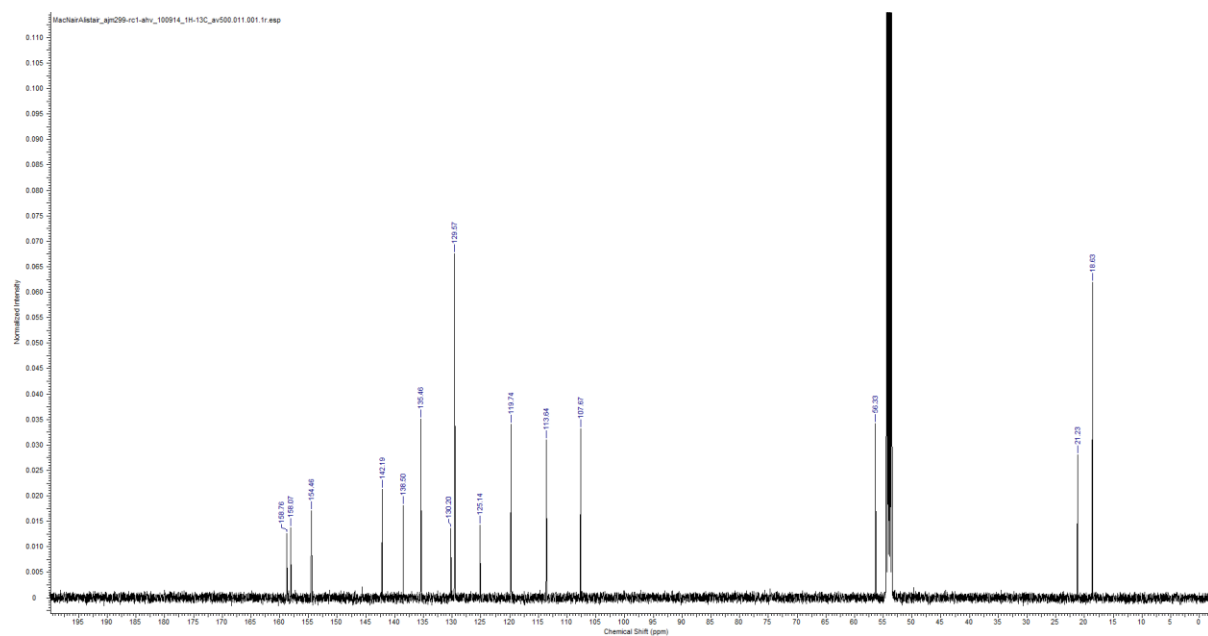
**Ethanediame, *N*-(2-hydroxy-, 5-methoxyphenyl)-*N'*-(2,4,6-trimethylphenyl)- (235)**



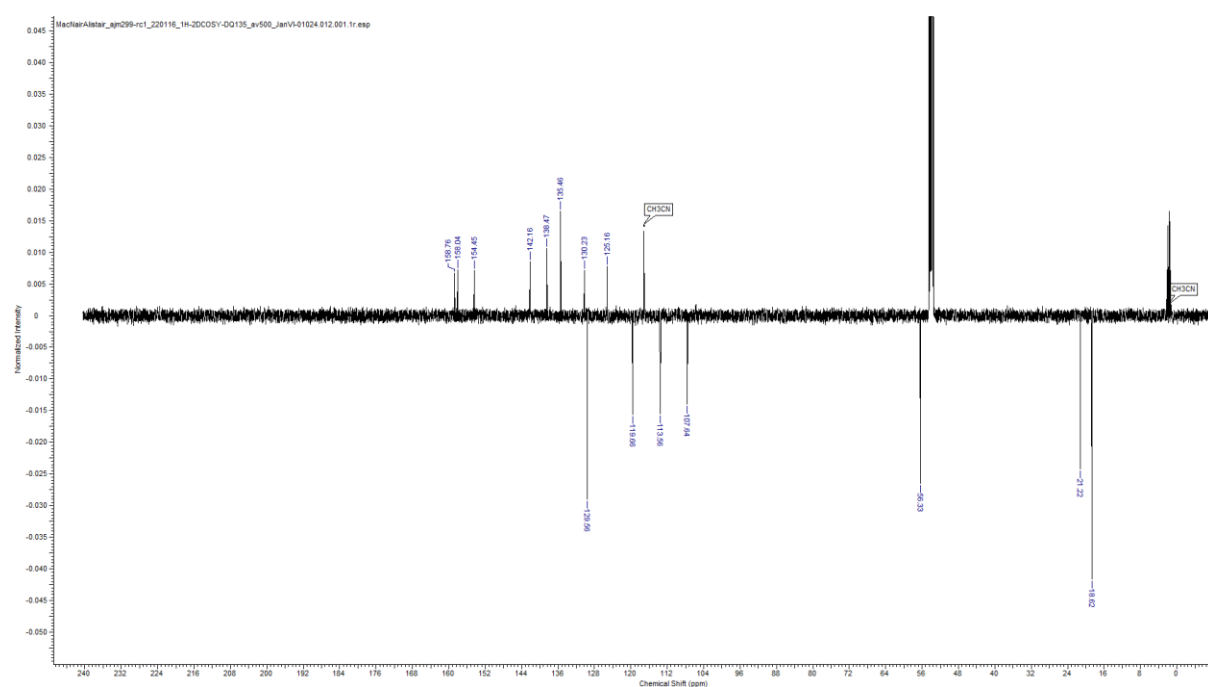
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



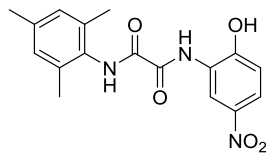
$^{13}\text{C}$ , 125 MHz,  $\text{CD}_2\text{Cl}_2$



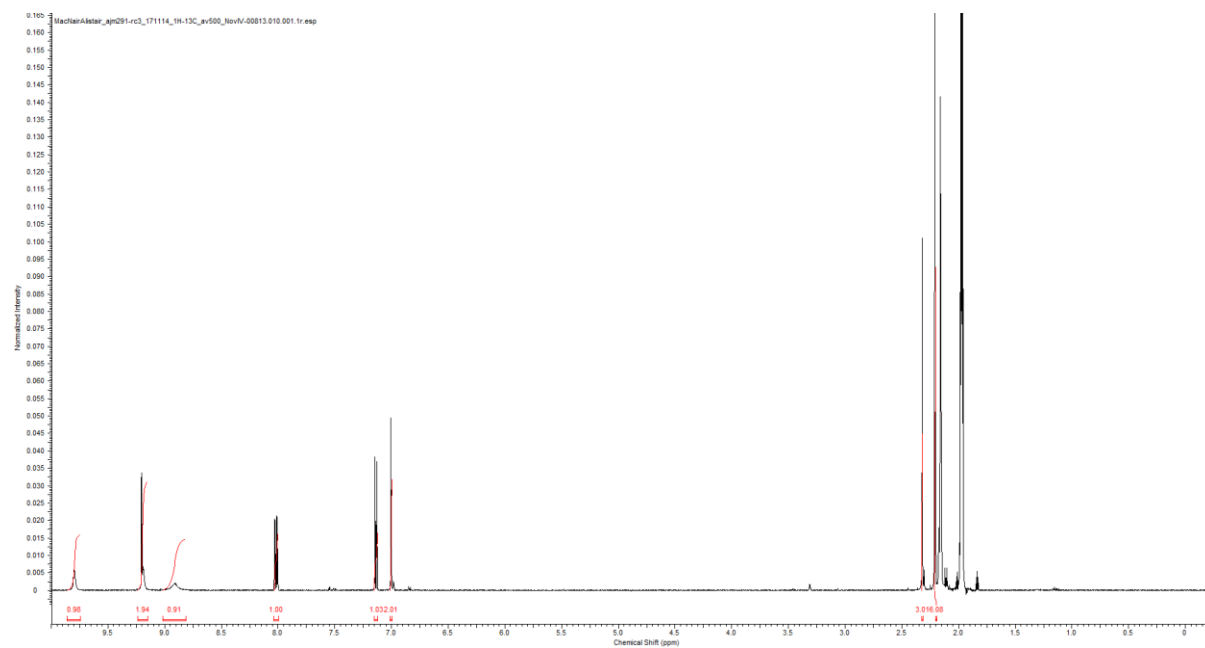
$^{13}\text{C}$  DEPT 135 (with quaternary), 125 MHz,  $\text{CD}_2\text{Cl}_2$



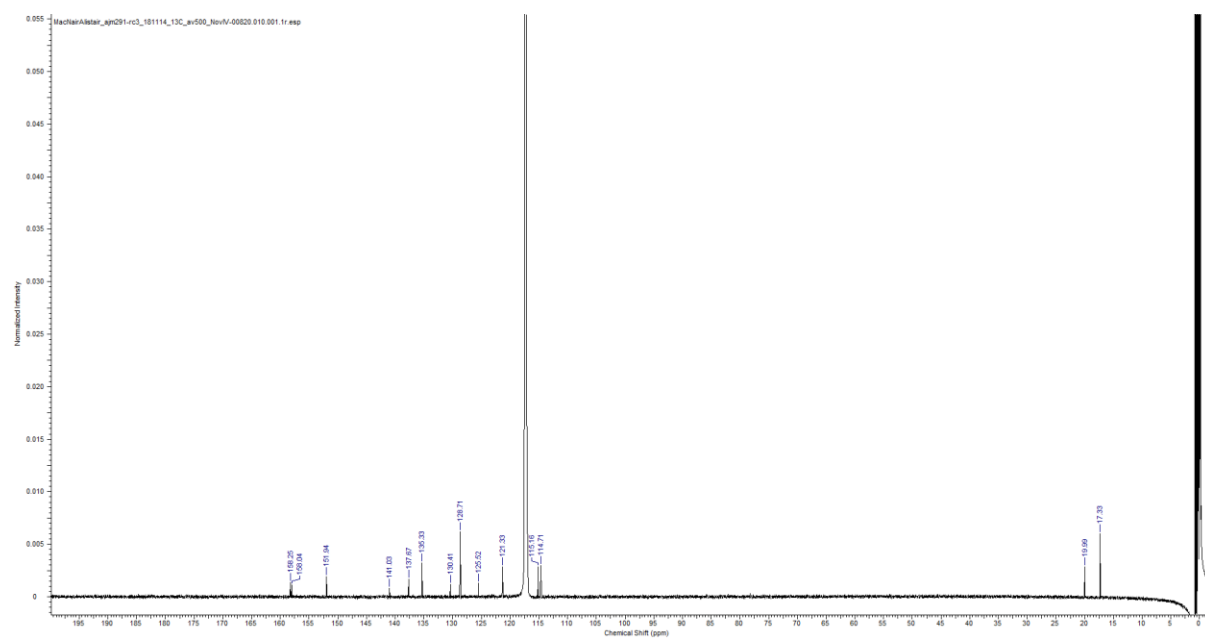
**Ethanediamide, *N*-(2-hydroxy-, 5-nitrophenyl)-*N'*-(2,4,6-trimethylphenyl)- (236)**



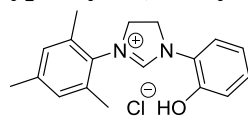
<sup>1</sup>H, 500 MHz, CD<sub>3</sub>CN



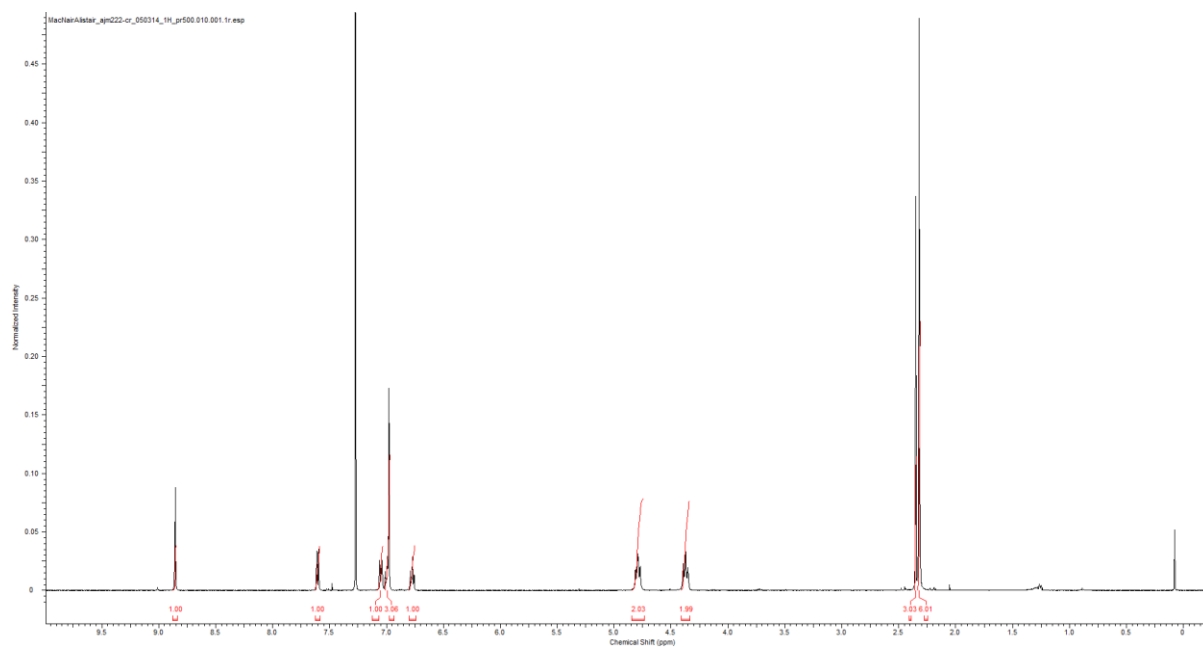
<sup>13</sup>C, 126 MHz, CD<sub>3</sub>CN



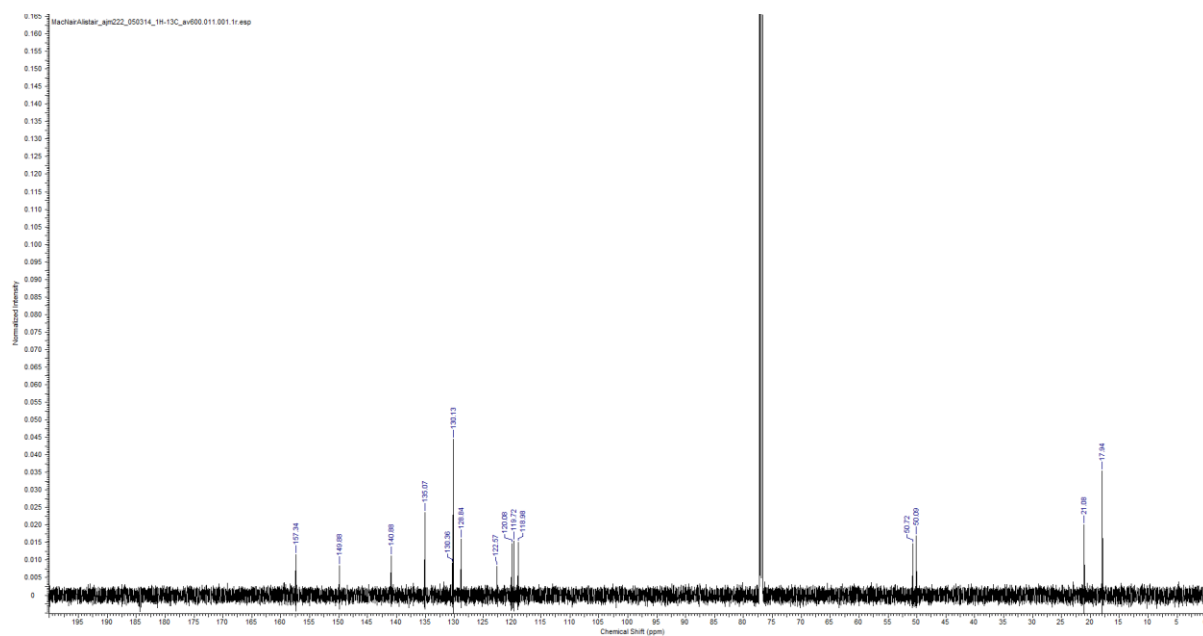
**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride (237)**



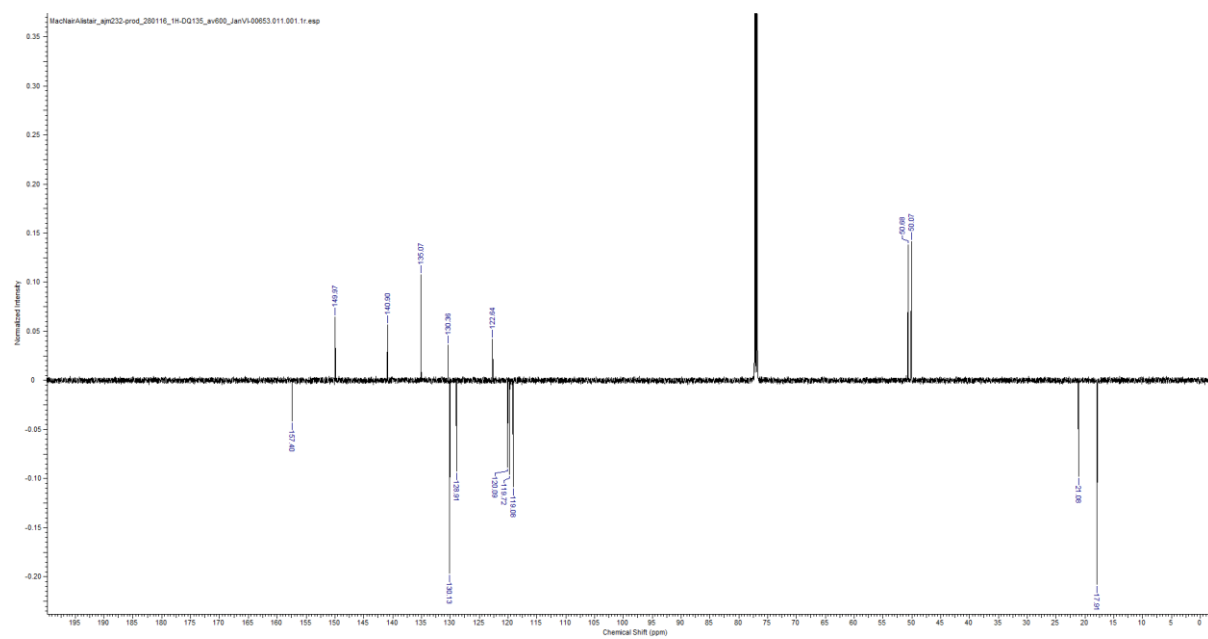
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



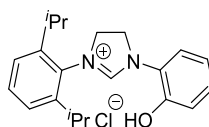
$^{13}\text{C}$ , 125 MHz,  $\text{CDCl}_3$



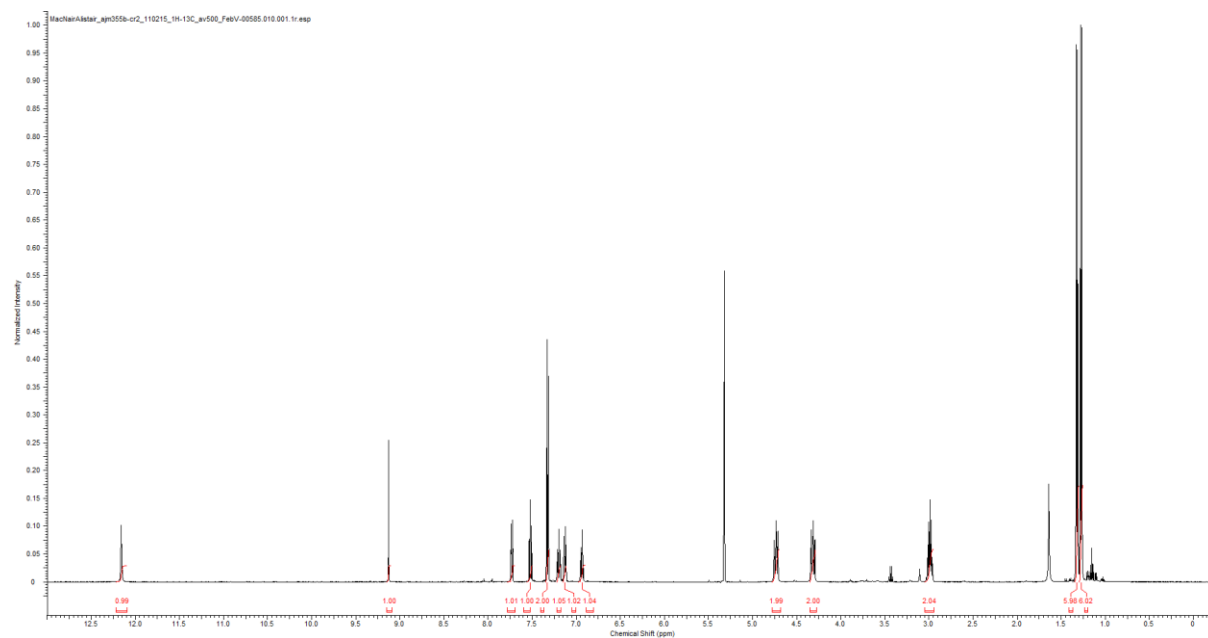
$^{13}\text{C}$  DEPT (with quaternary), 150 MHz,  $\text{CDCl}_3$



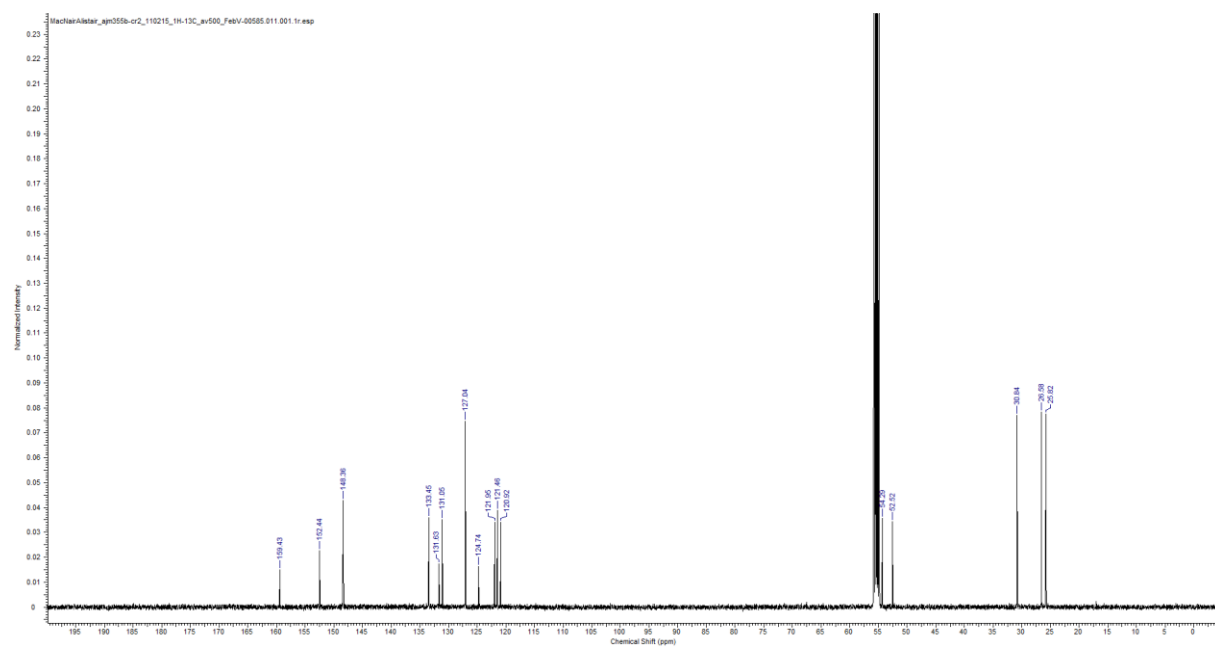
# 1-(2, 6-Diisopropylphenyl)-3-(2-hydroxyphenyl)-4,5-dihydro-imidazolium chloride (238)



$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$

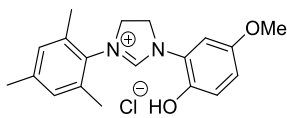


$^{13}\text{C}$ , 125 MHz,  $\text{CD}_2\text{Cl}_2$

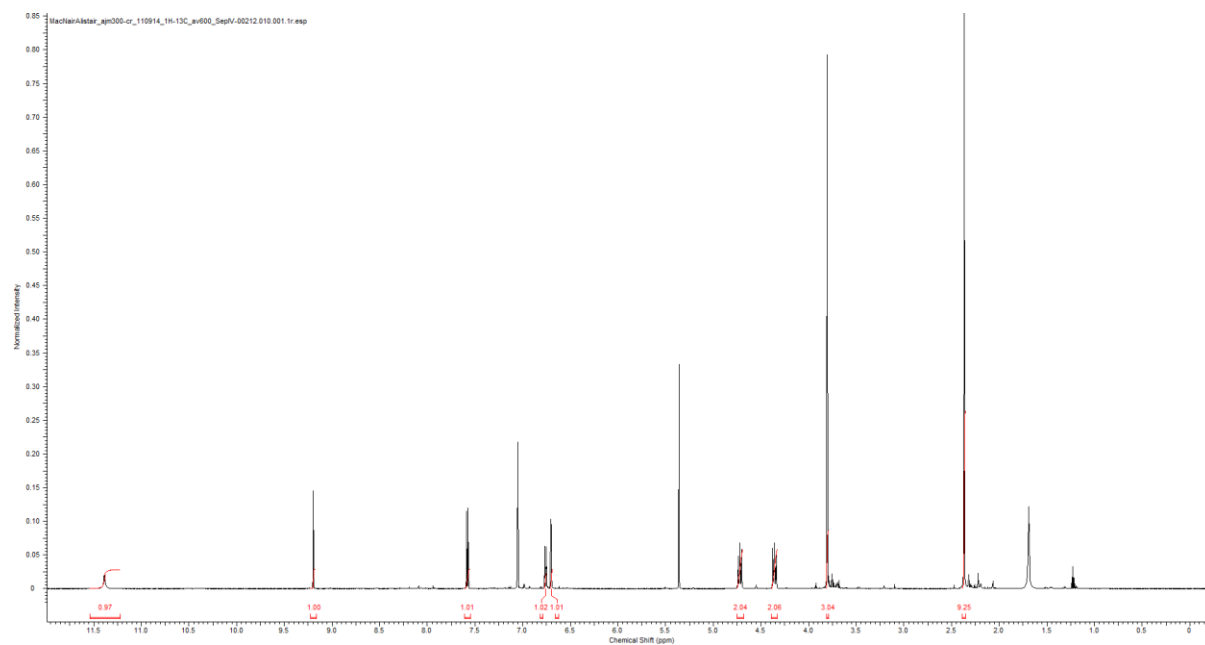




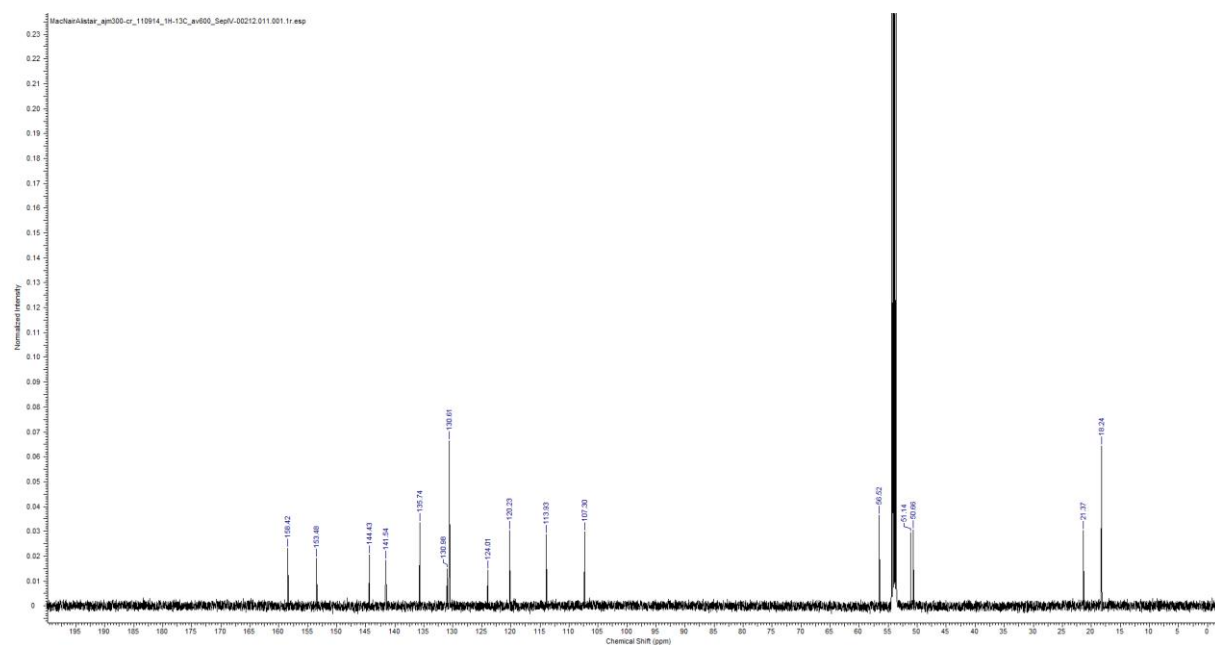
**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-, 5-methoxyphenyl)-4,5-dihydro-imidazolium chloride (239)**



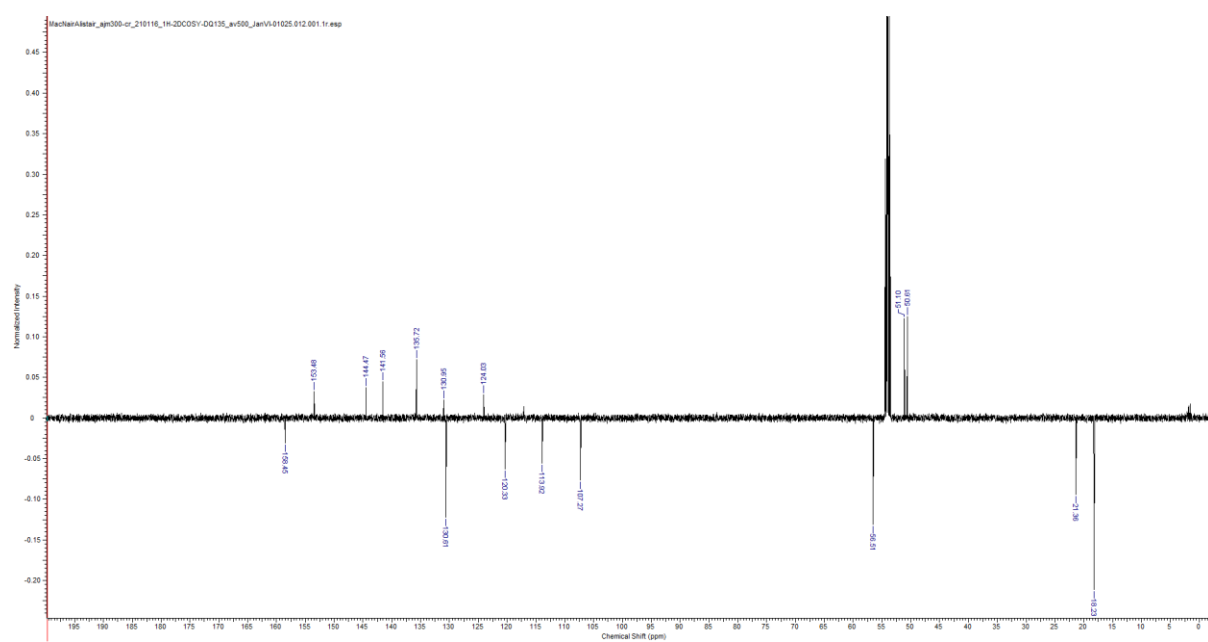
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



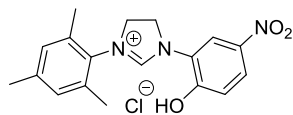
$^{13}\text{C}$ , 125 MHz,  $\text{CD}_2\text{Cl}_2$



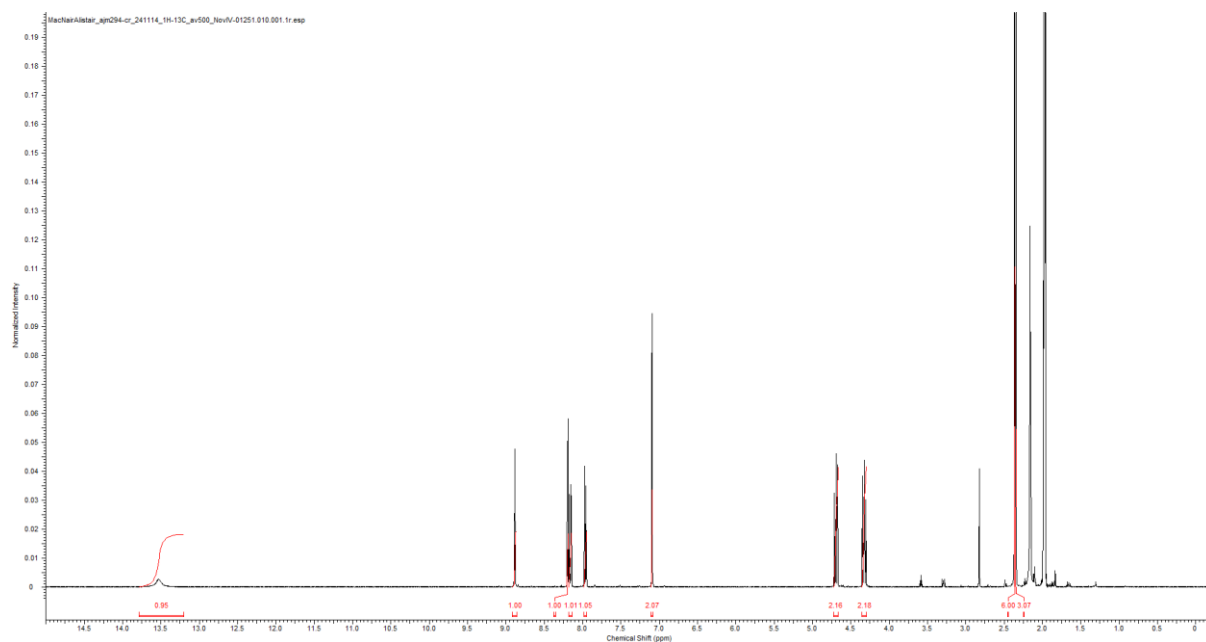
$^{13}\text{C}$  DEPT 135 (with quaternary), 125 MHz,  $\text{CD}_2\text{Cl}_2$



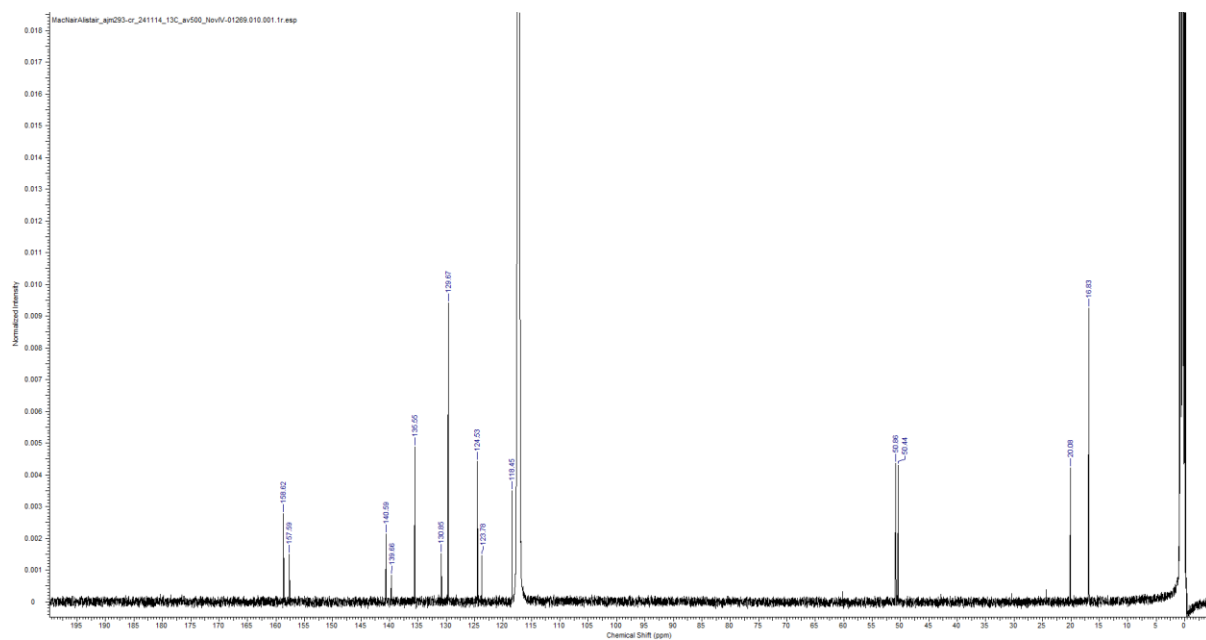
# 1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-, 5-nitrophenyl)-4,5-dihydro-imidazolium chloride (240)



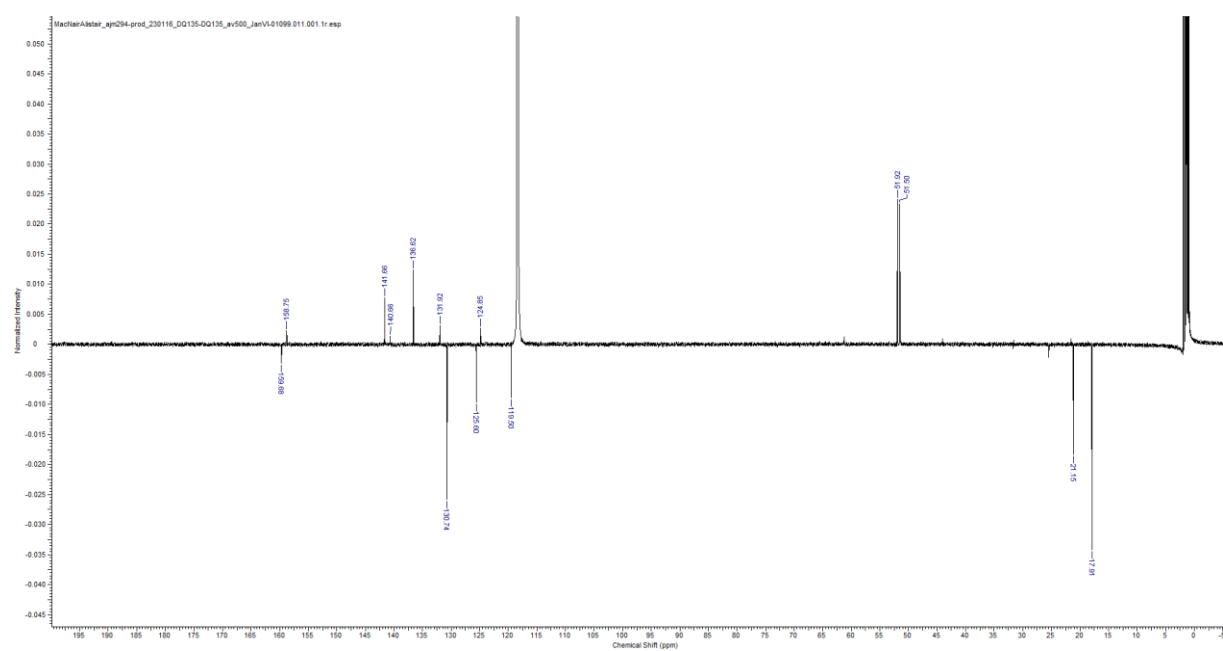
$^1\text{H}$ , 500 MHz,  $\text{CD}_3\text{CN}$



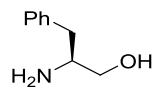
$^{13}\text{C}$ , 125 MHz,  $\text{CD}_3\text{CN}$



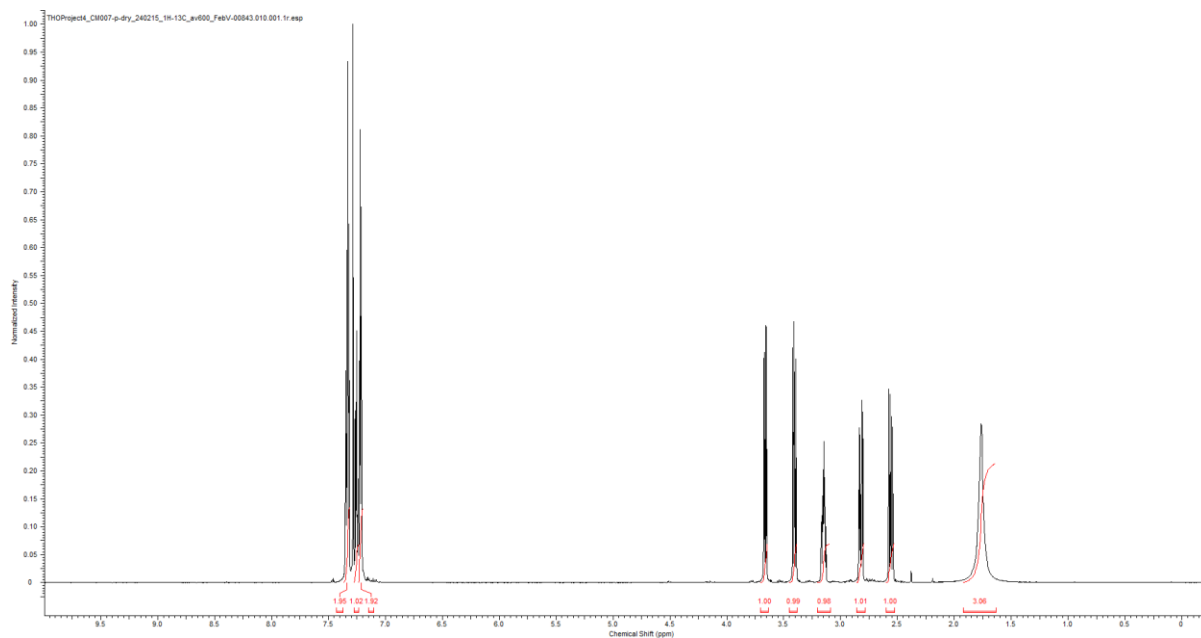
$^{13}\text{C}$  DEPT 135, 125 MHz,  $\text{CD}_3\text{CN}$



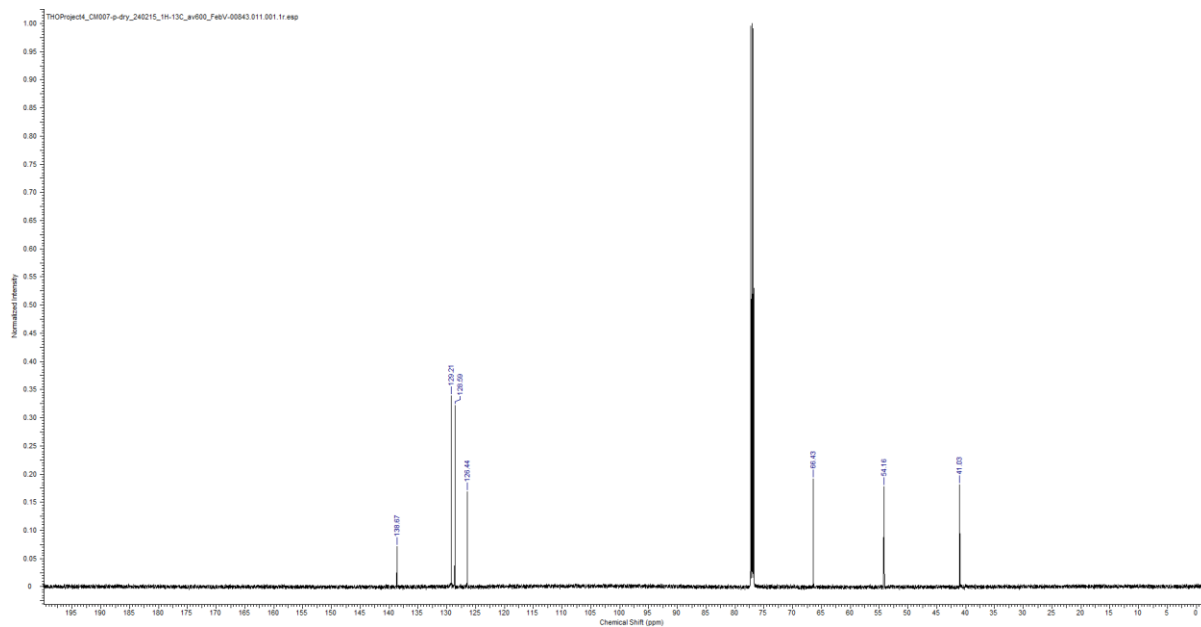
**(S)-(+)-2-Amino-3-phenyl-1-propanol**



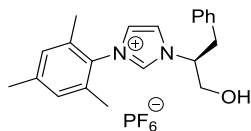
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



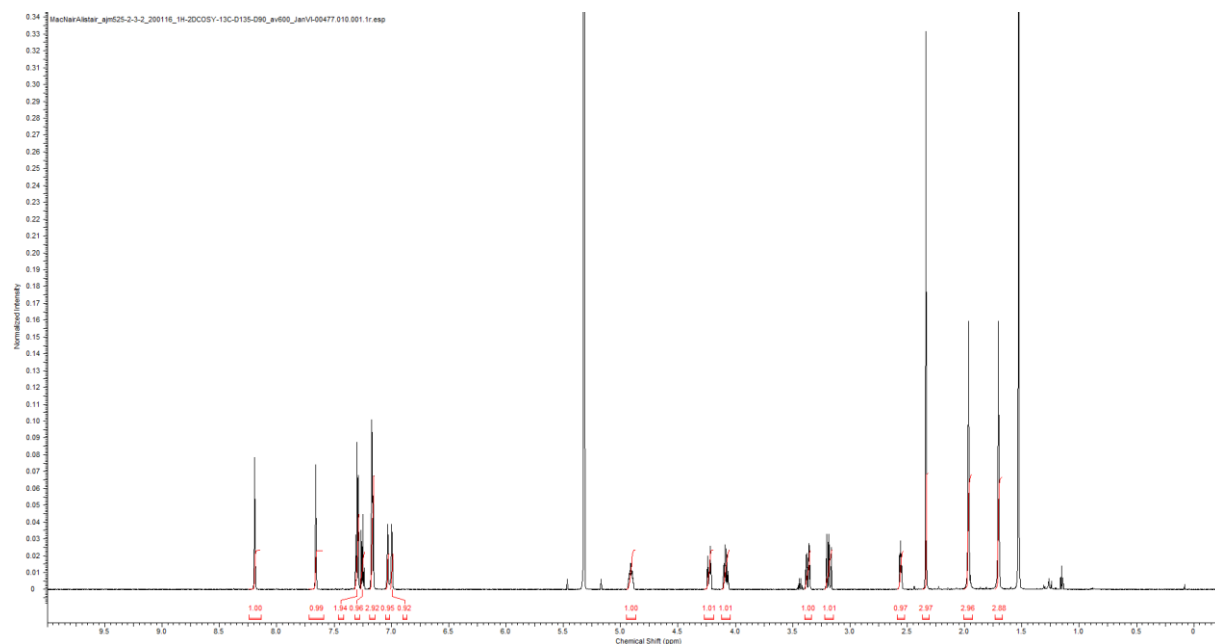
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



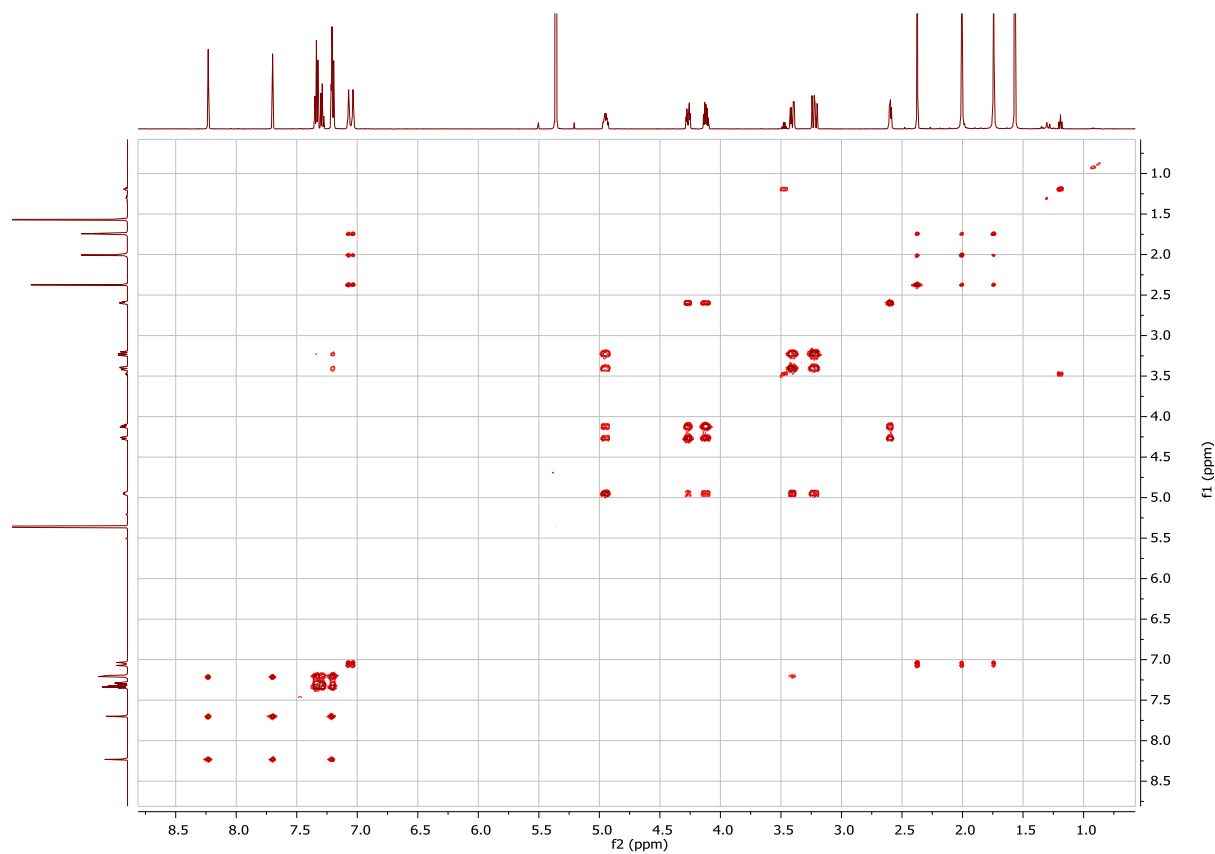
**1-(2,4,6-Trimethylphenyl)-3-[(S)-2N-3-phenylpropanol]-imidazolium hexafluorophosphate (242)**



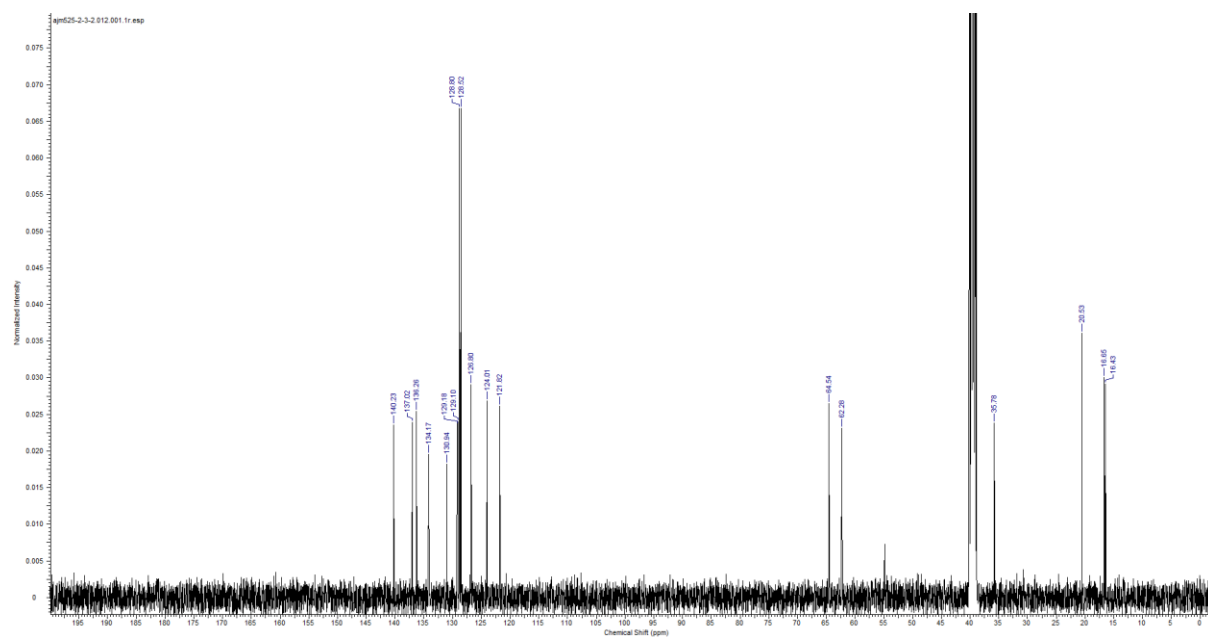
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



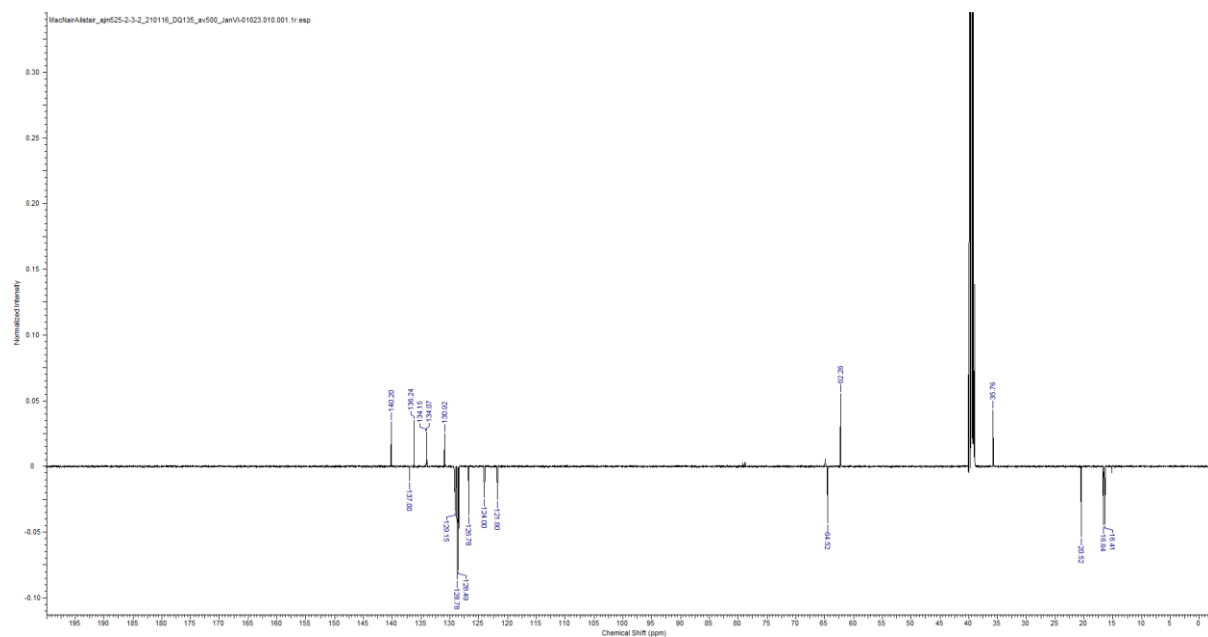
$^1\text{H}$  COSY, 600 MHz,  $\text{CD}_2\text{Cl}_2$



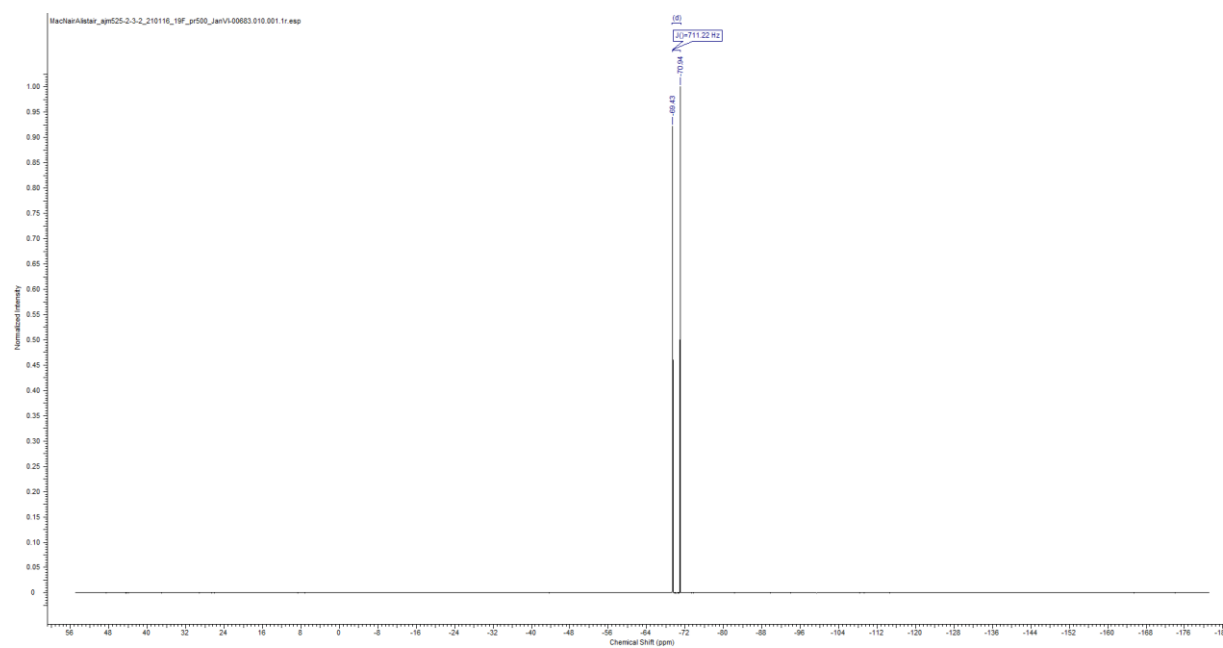
$^{13}\text{C}$ , 100 MHz,  $(\text{CD}_3)_2\text{SO}$



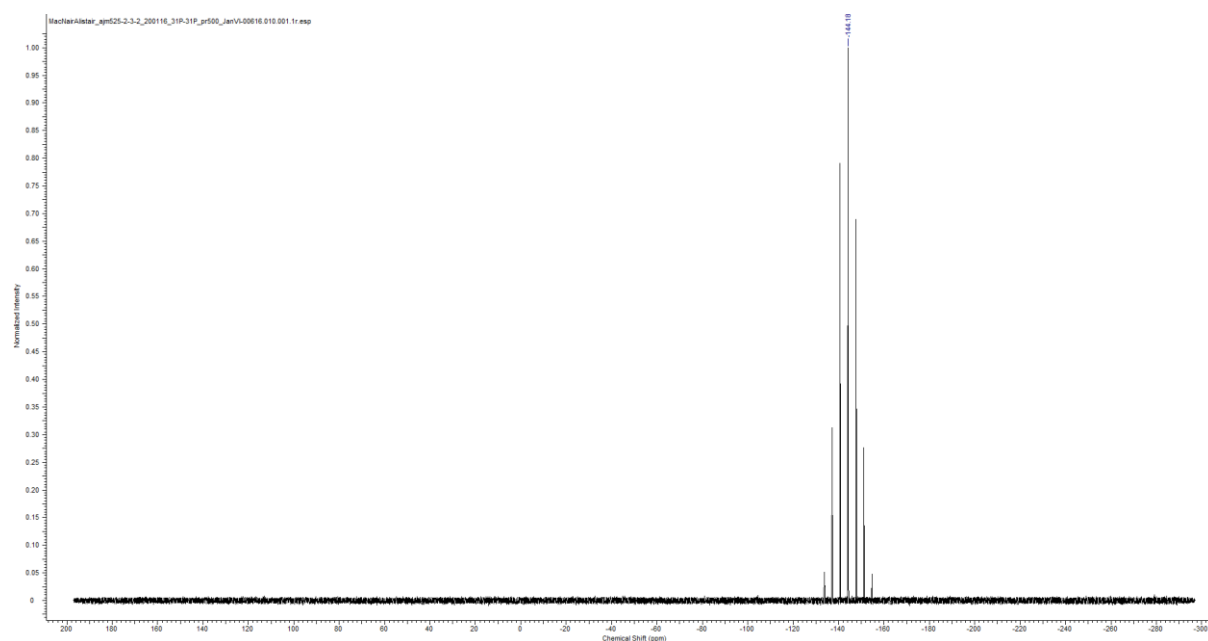
$^{13}\text{C}$  DEPT 135 (with quaternary), 126 MHz,  $(\text{CD}_3)_2\text{SO}$



$^{19}\text{F}$ , 471 MHz,  $(\text{CD}_3)_2\text{SO}$

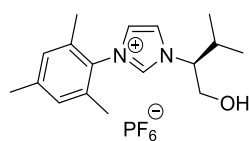


$^{31}\text{P}$  NMR, 203 MHz,  $(\text{CD}_3)_2\text{SO}$

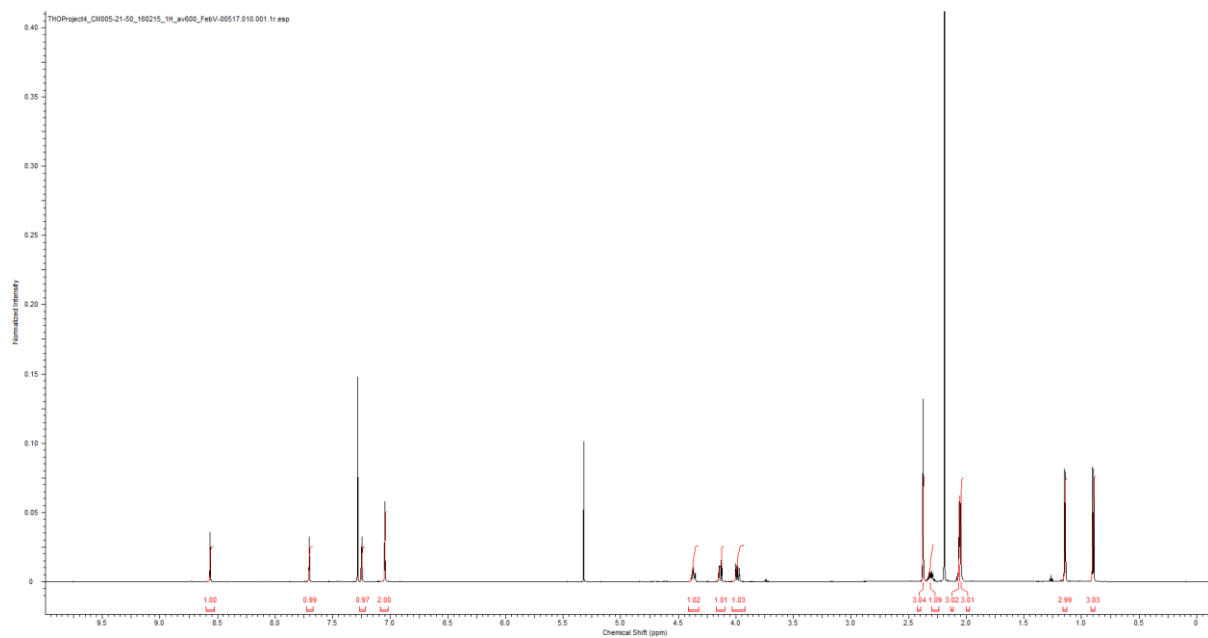




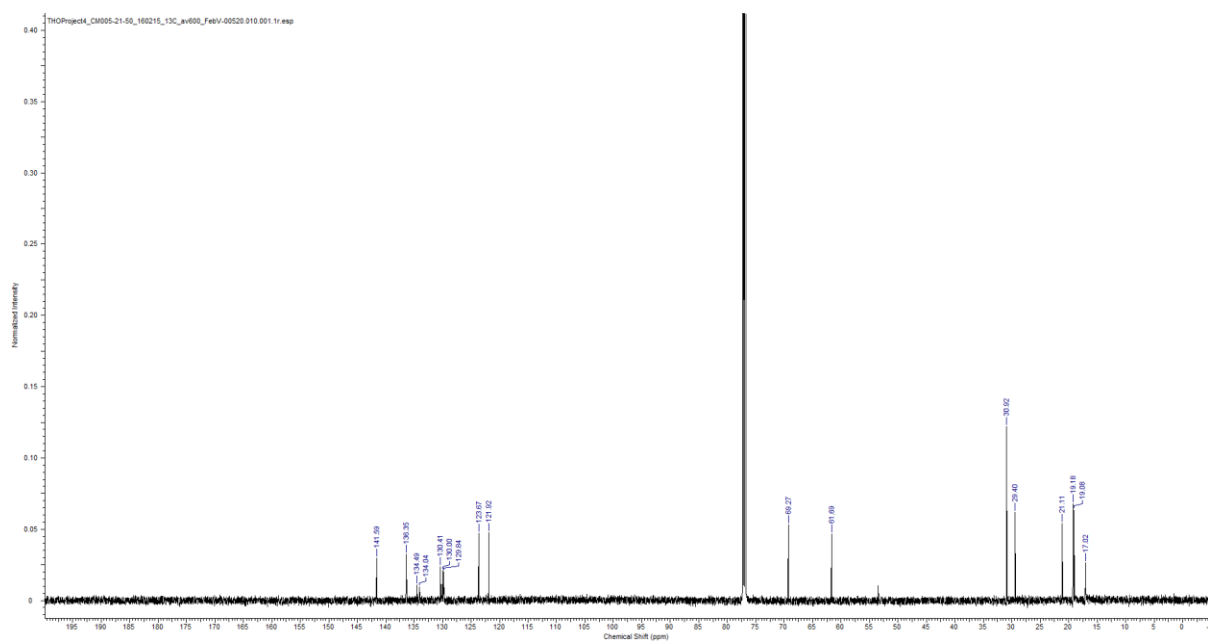
**1-(2,4,6-Trimethylphenyl)-3-((*S*)-2N-3-methylbutanol)-imidazolium hexafluorophosphate (244)**



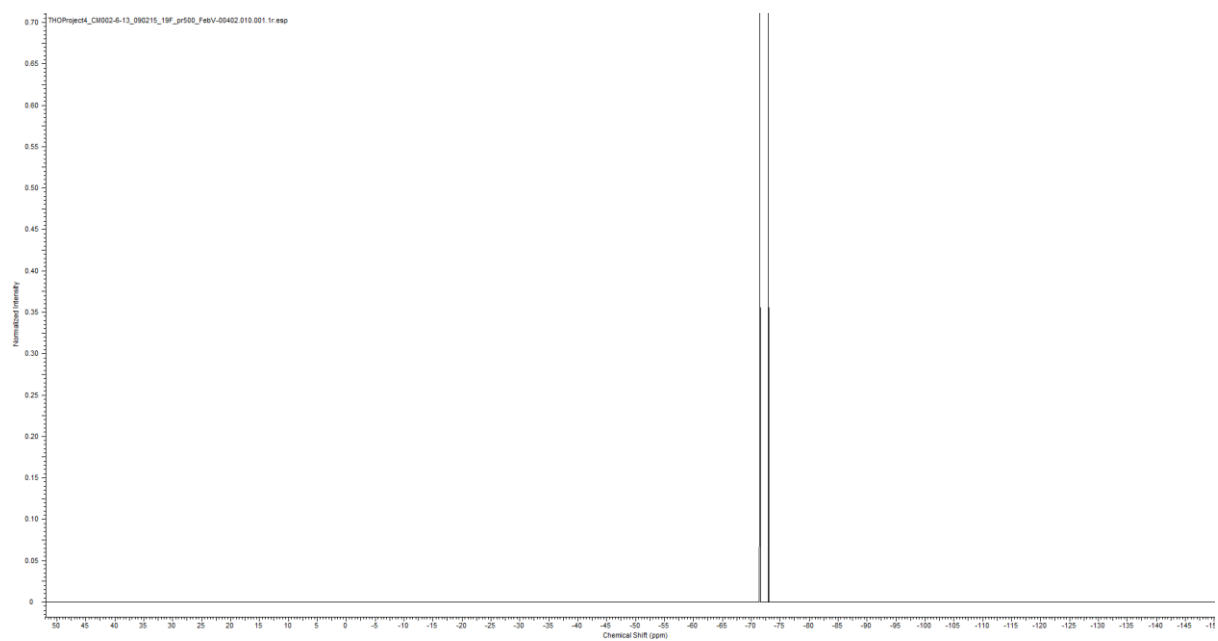
$^1\text{H}$ , 600 MHz,  $\text{CDCl}_3$



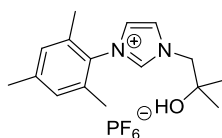
$^{13}\text{C}$ , 150 MHz,  $\text{CDCl}_3$



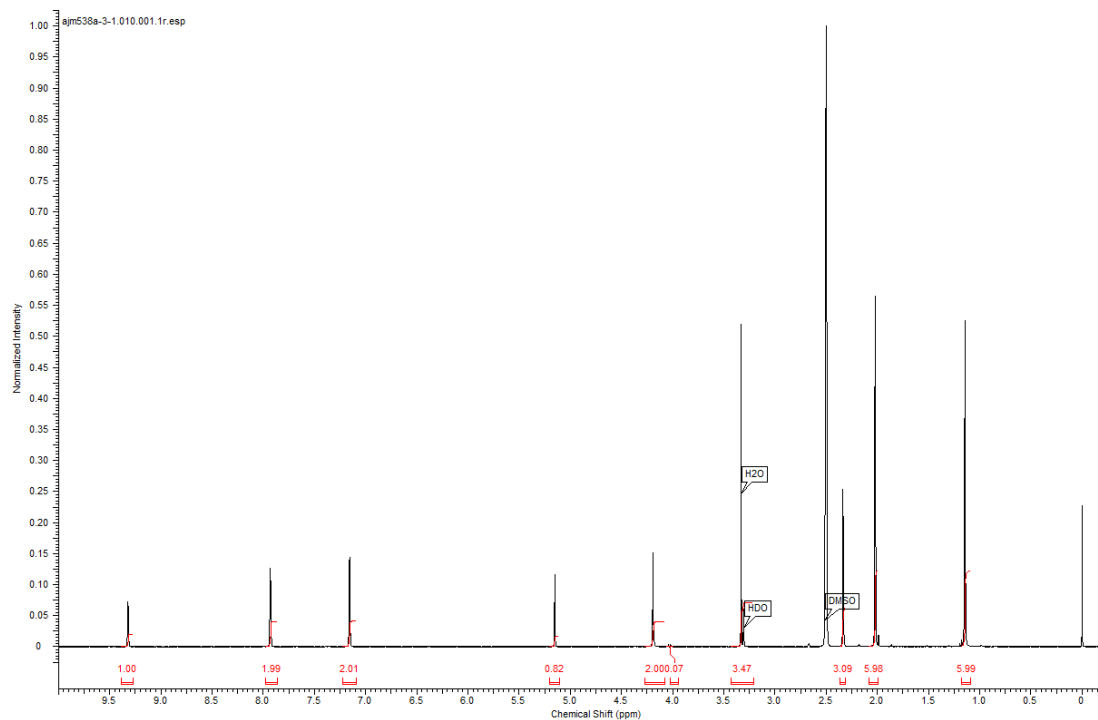
$^{19}\text{F}$ , 470 MHz,  $\text{CDCl}_3$



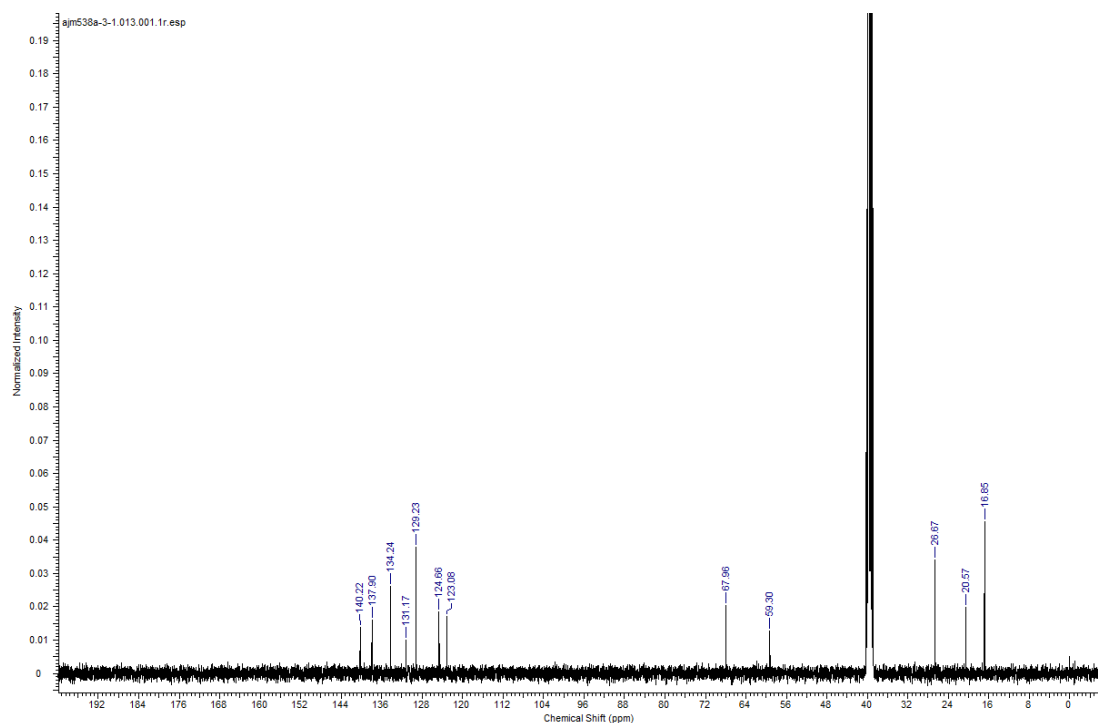
**1-(2,4,6-Trimethylphenyl)-3-(2-hydroxy-2-methylpropyl)-imidazolium hexafluorophosphate (245)**



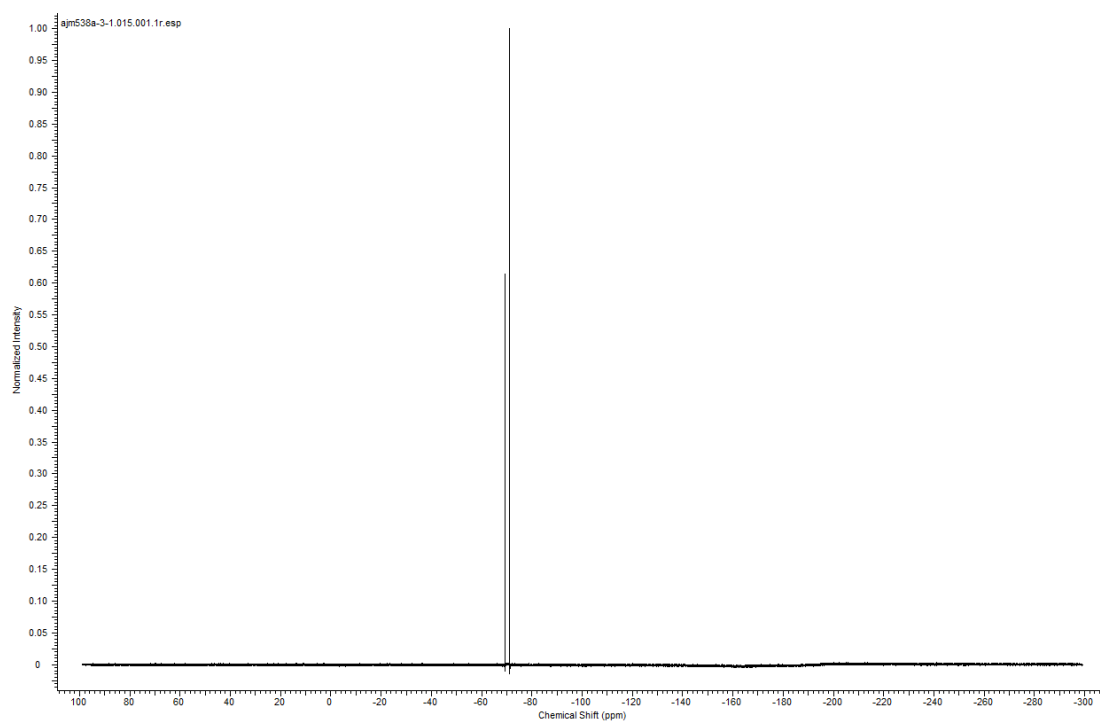
$^1\text{H}$ , 400 MHz,  $(\text{CD}_3)_2\text{SO}$



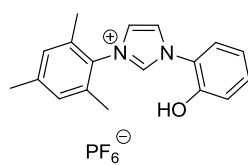
$^{13}\text{C}$ , 100 MHz,  $(\text{CD}_3)_2\text{SO}$



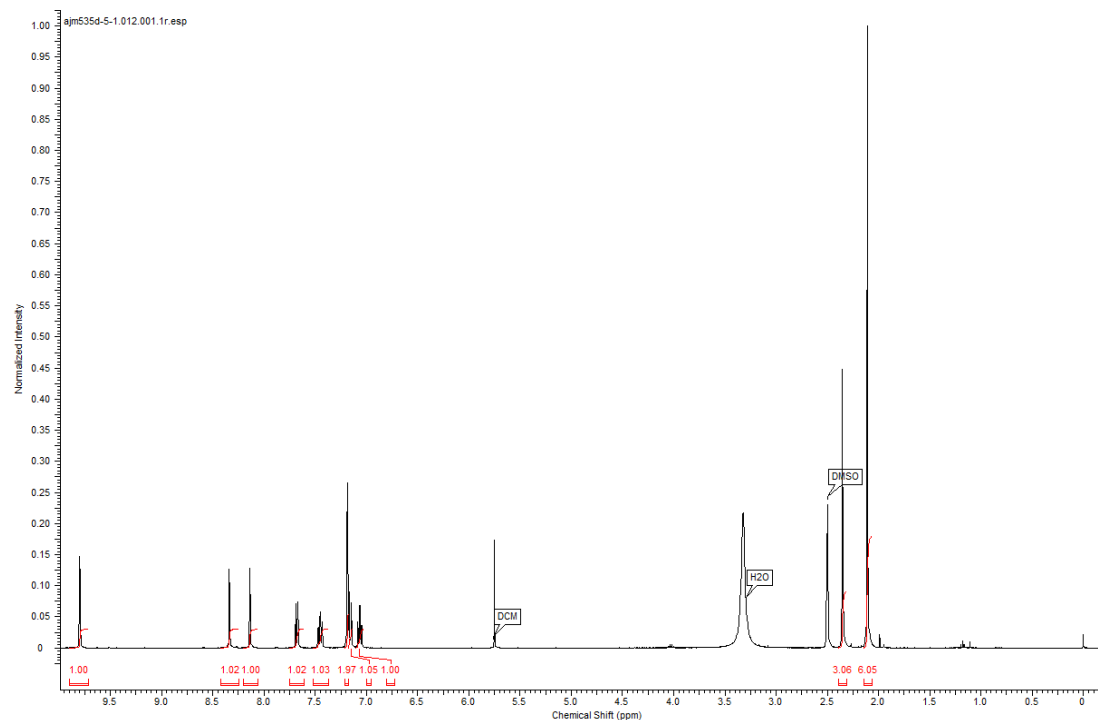
$^{19}\text{F}$ , 377 MHz,  $(\text{CD}_3)_2\text{SO}$



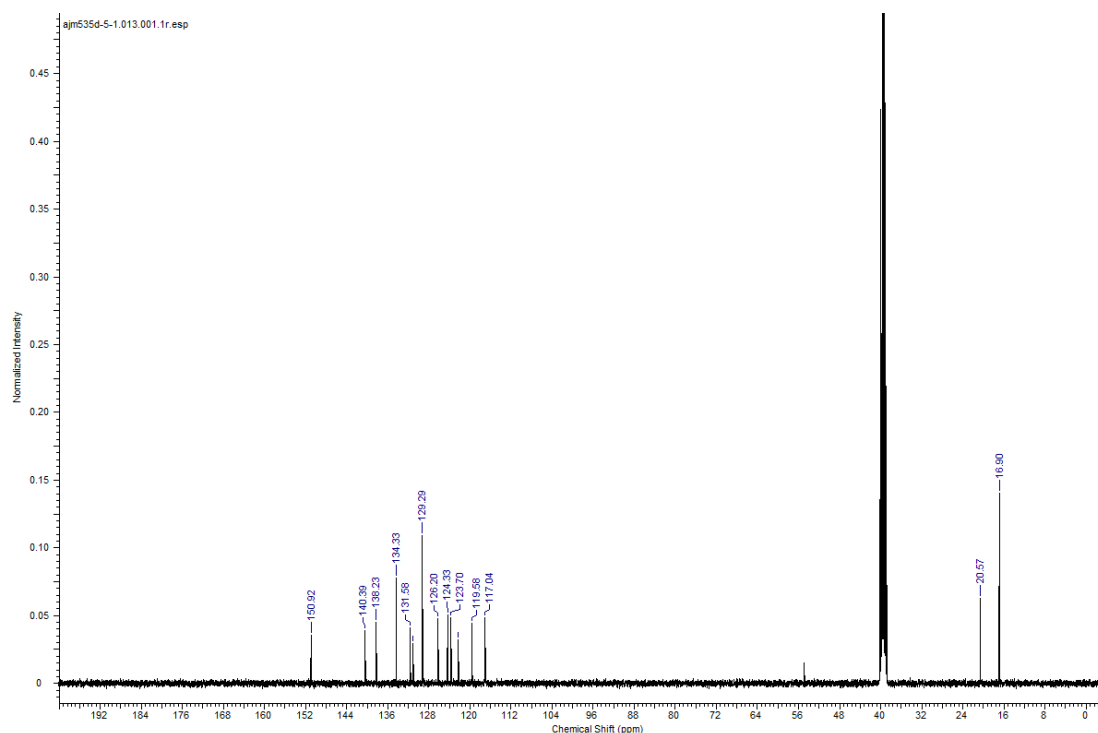
# 1-(2,4,6-Trimethylphenyl)-3-(2-hydroxyphenyl)-imidazolium hexafluorophosphate (246)



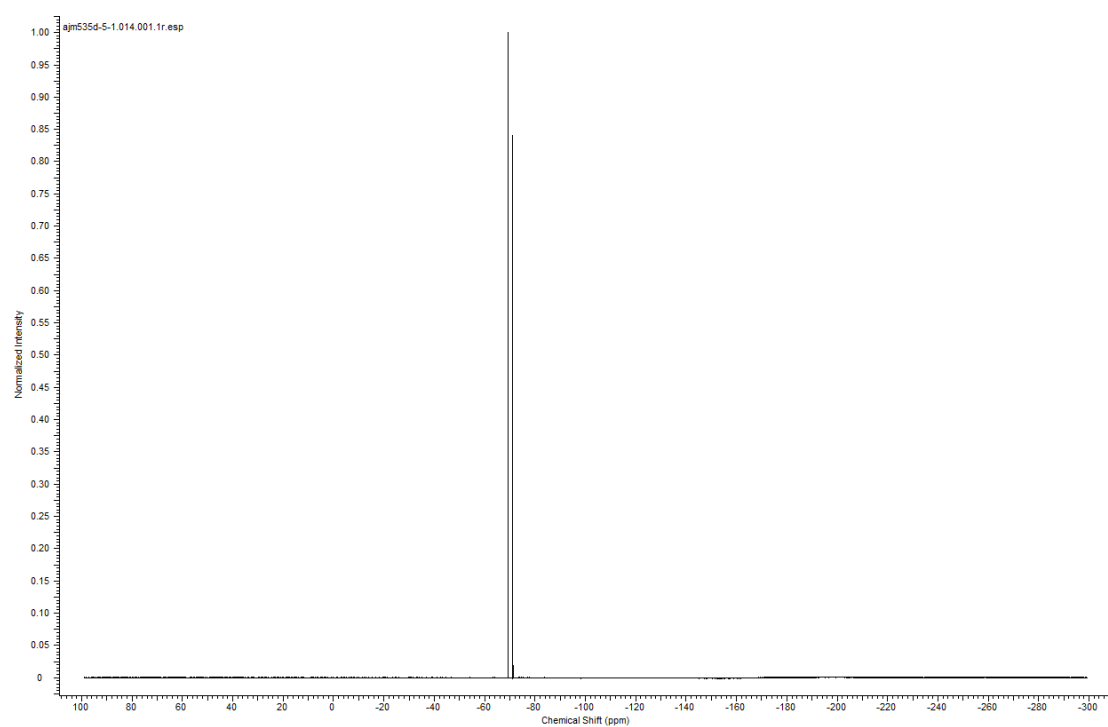
$^1\text{H}$ , 400 MHz,  $(\text{CD}_3)_2\text{SO}$



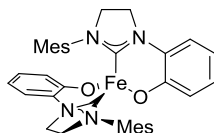
$^{13}\text{C}$ , 100 MHz,  $(\text{CD}_3)_2\text{SO}$



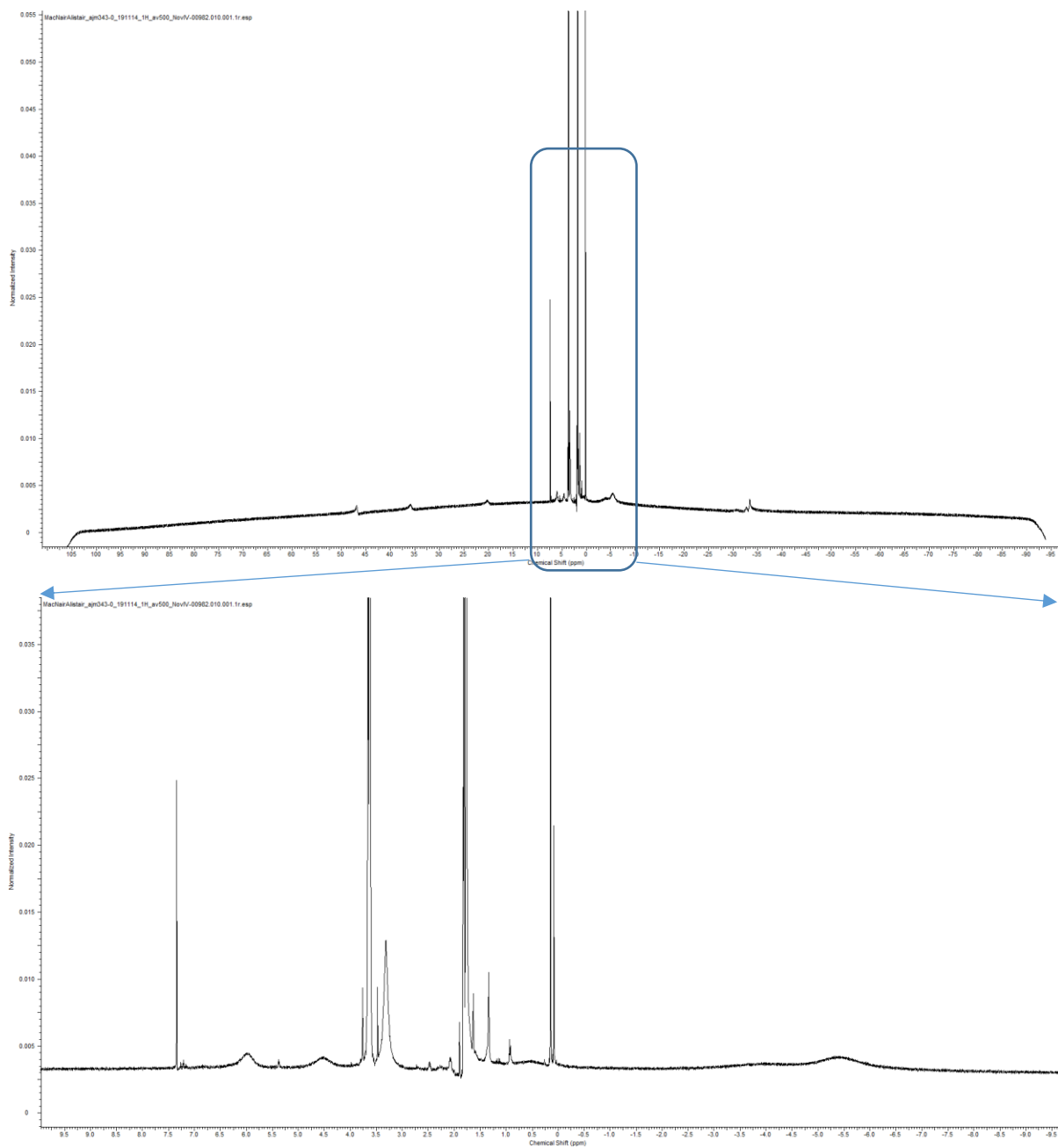
$^{19}\text{F}$ , 377 MHz,  $(\text{CD}_3)_2\text{SO}$



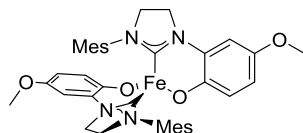
**Bis[1-(2,4,6-trimethylphenyl)-3-(2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) (250)**



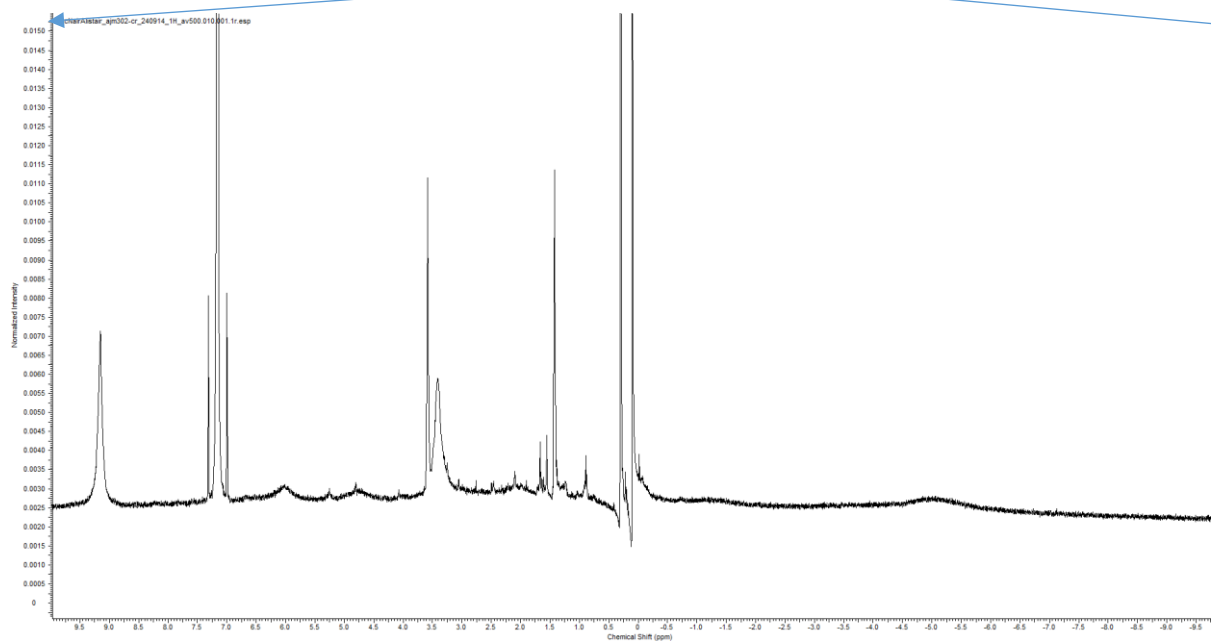
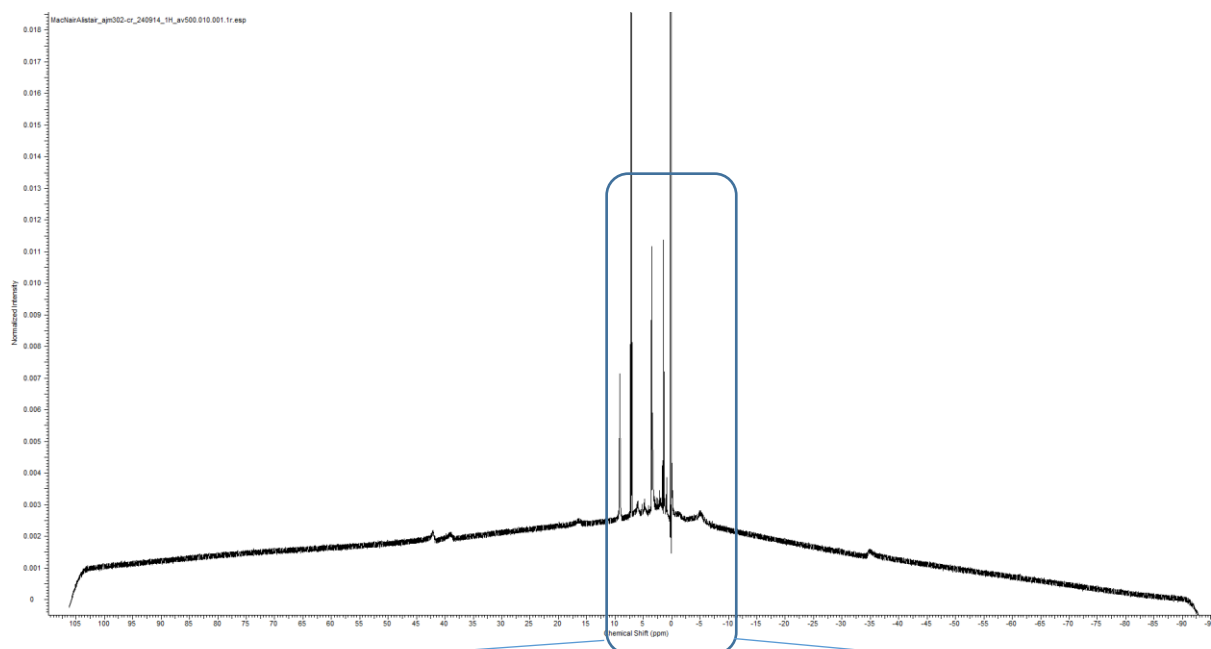
$^1\text{H}$ , 500 MHz,  $d_8$ -THF



**Bis[1-(2,4,6-trimethylphenyl)-3-(5-methoxy-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) (251)**

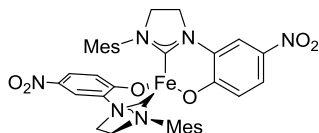


$^1\text{H}$ , 500 MHz,  $\text{C}_6\text{D}_6$

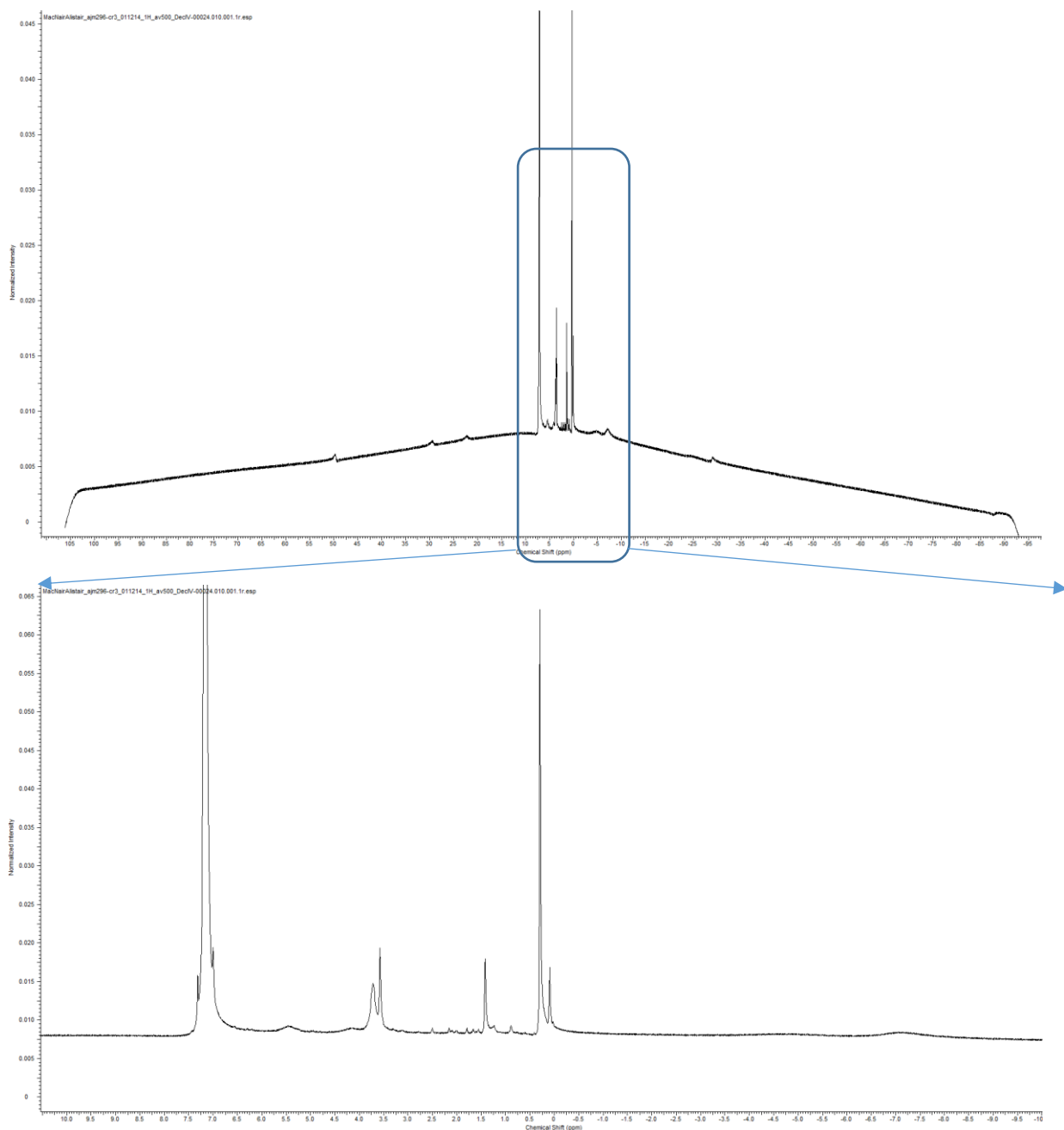




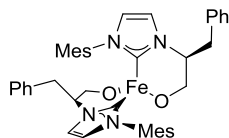
**Bis[1-(2,4,6-trimethylphenyl)-3-(5-nitro-2-phenoxy)-4,5-dihydro-imidazolyl] iron(II) (252)**



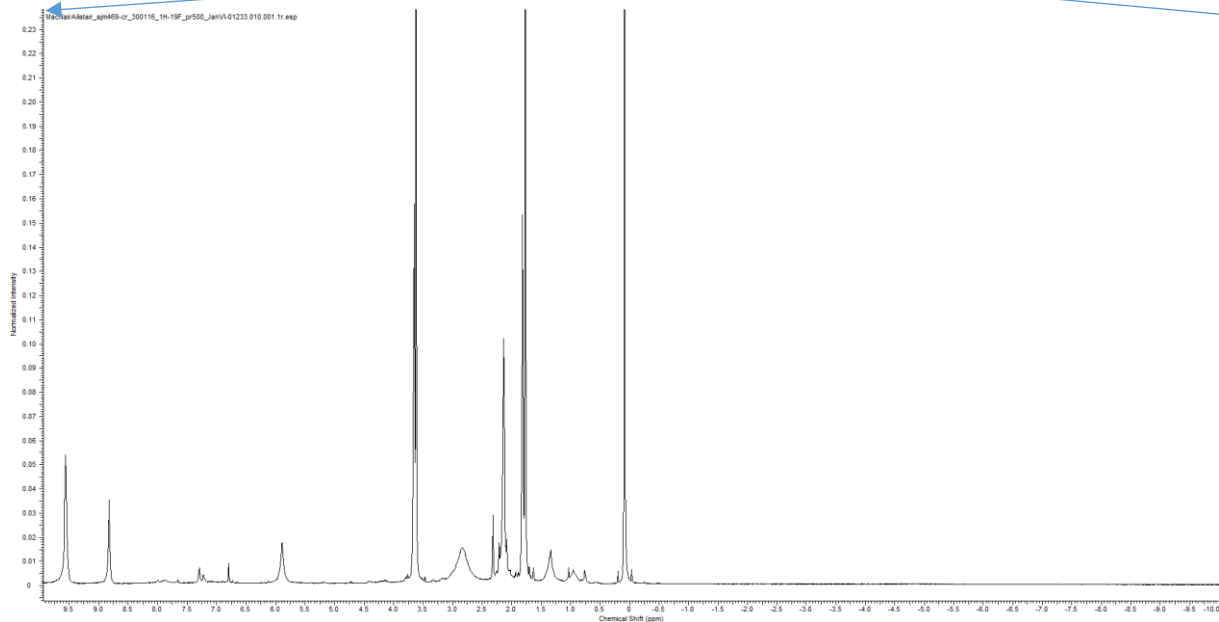
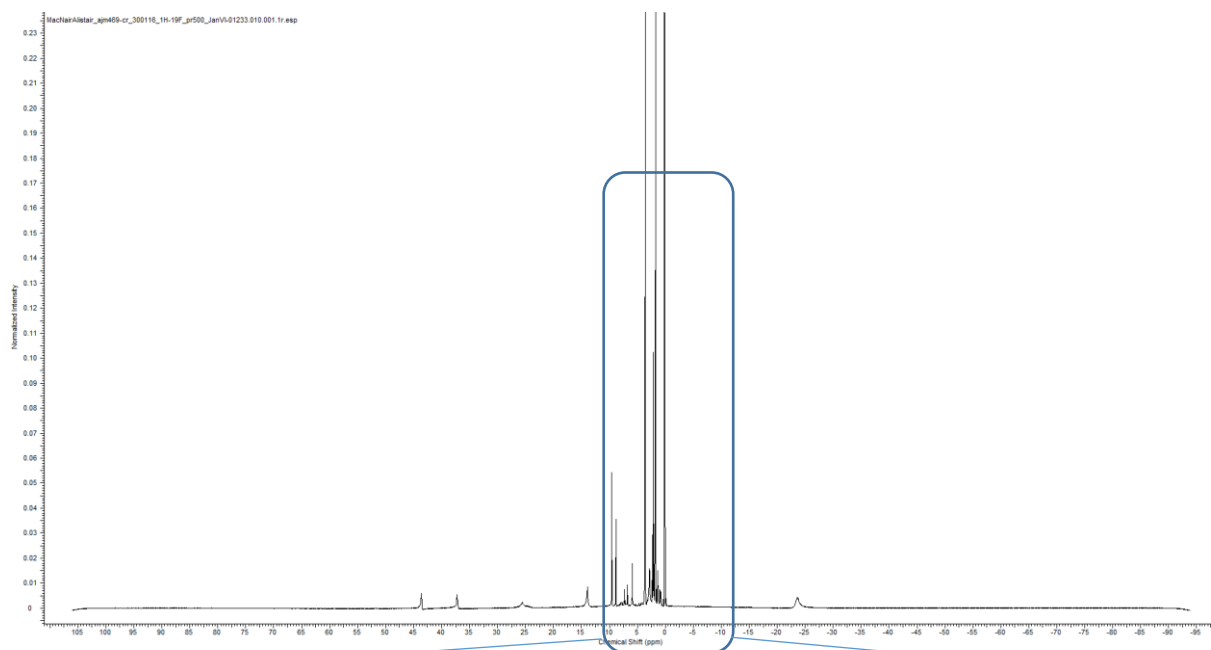
$^1\text{H}$ , 500 MHz,  $\text{C}_6\text{D}_6$



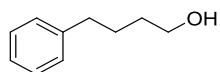
**Bis{1-[2,4,6-trimethylphenyl]-3-[(*S*)-2*N*-3-phenylpropanoxy]imidazolyl} iron(II) (253)**



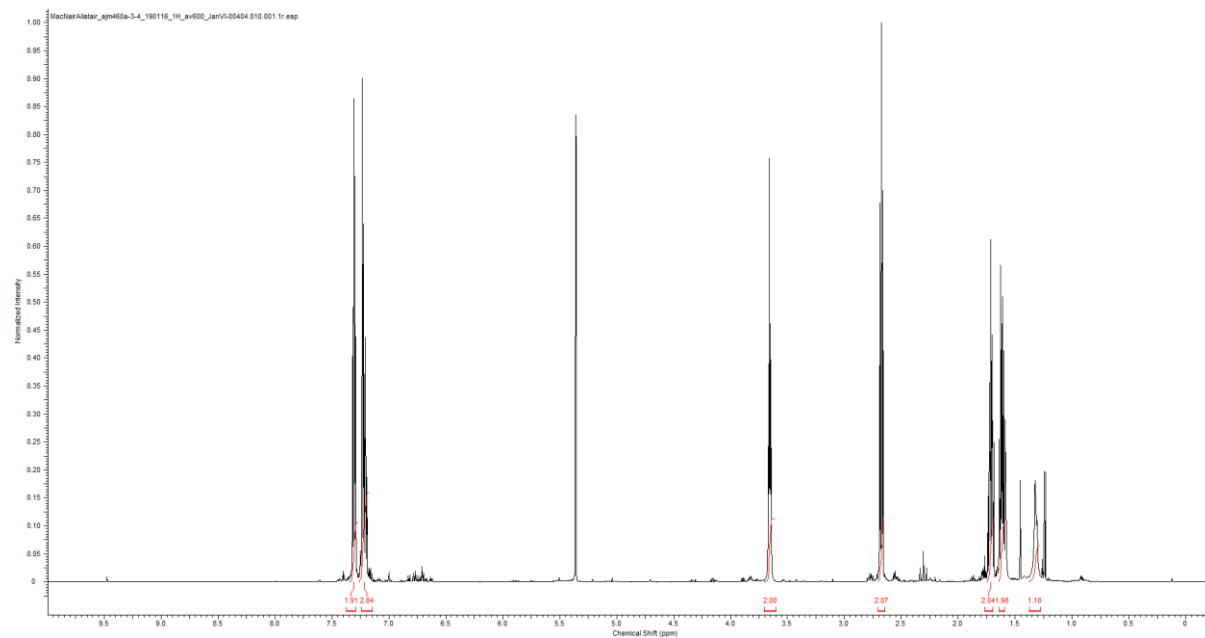
$^1\text{H}$ , 500 MHz,  $d_8$ -THF



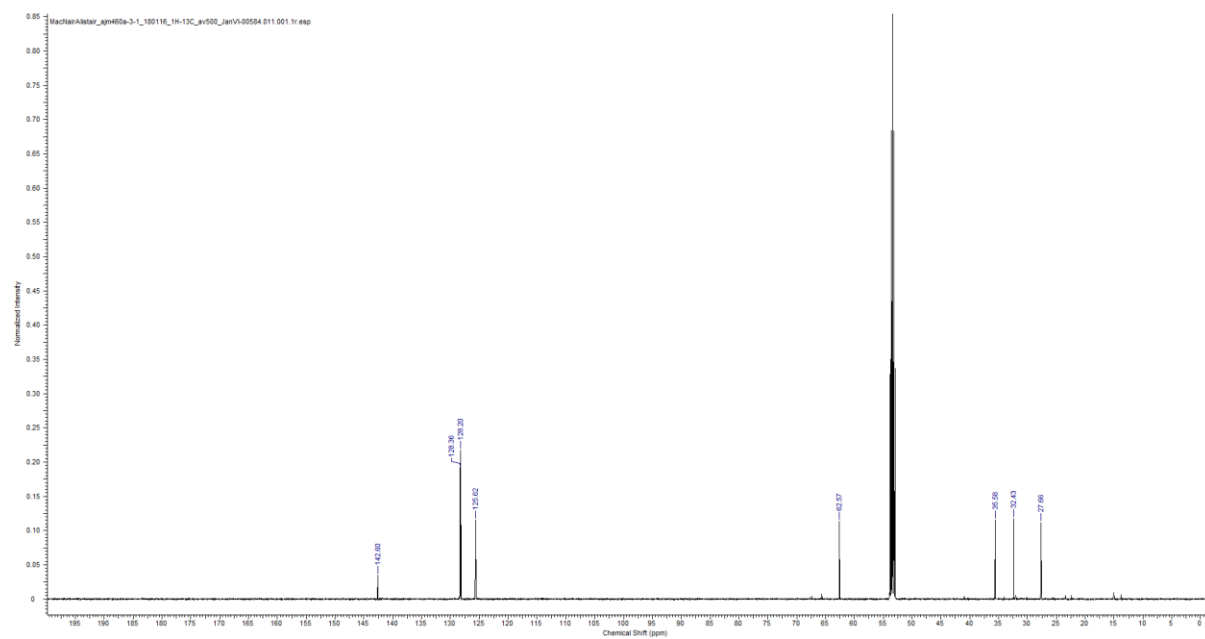
## Phenylbutan-1-ol (260)



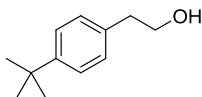
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



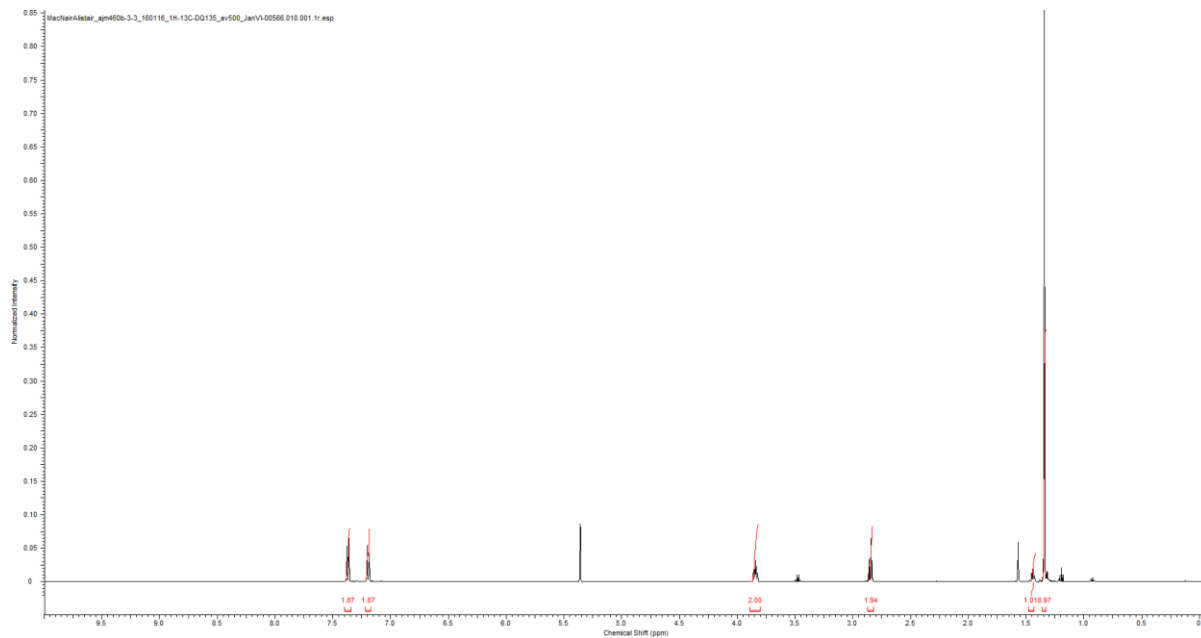
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



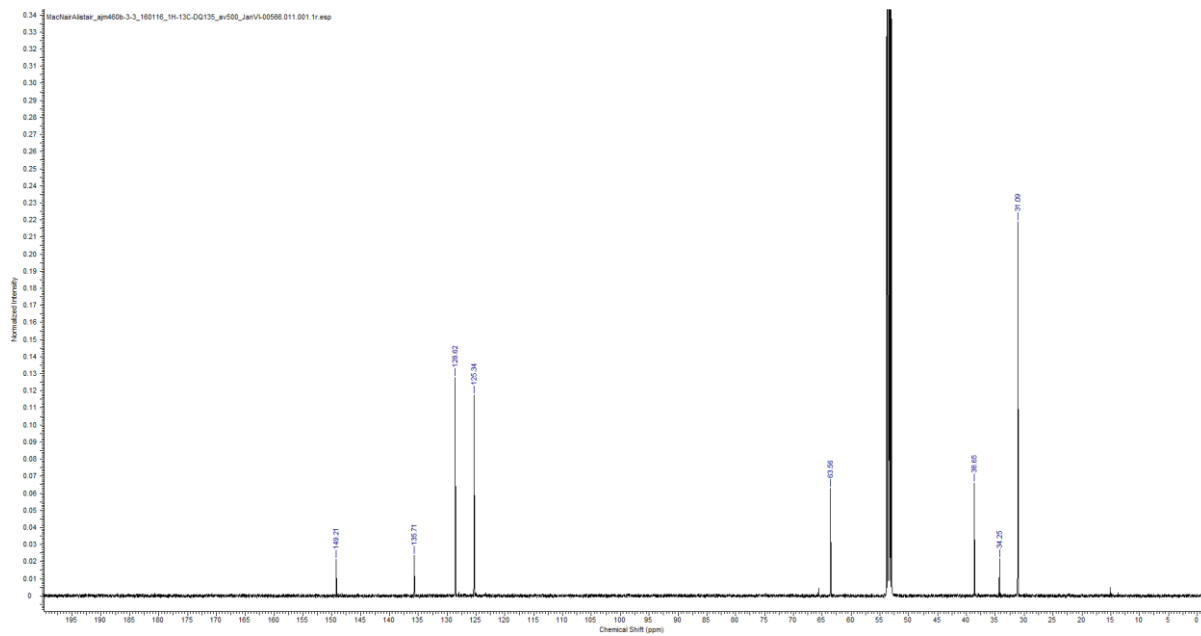
## 2-(4-*tert*-Butylphenyl)ethan-1-ol (262)



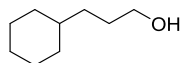
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



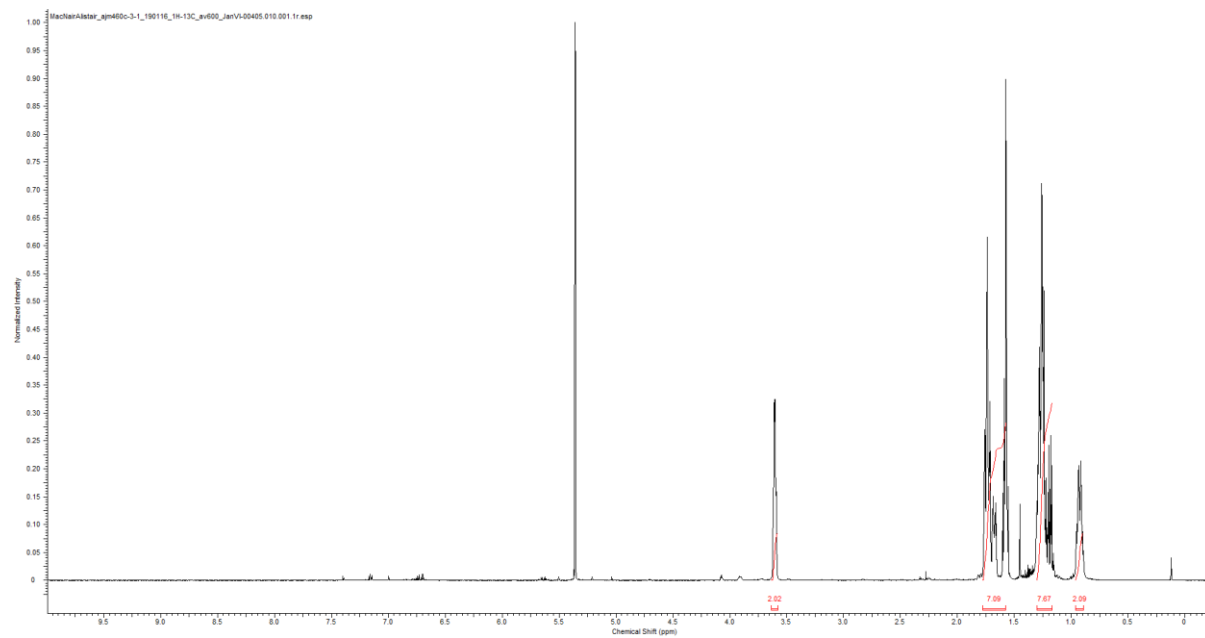
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



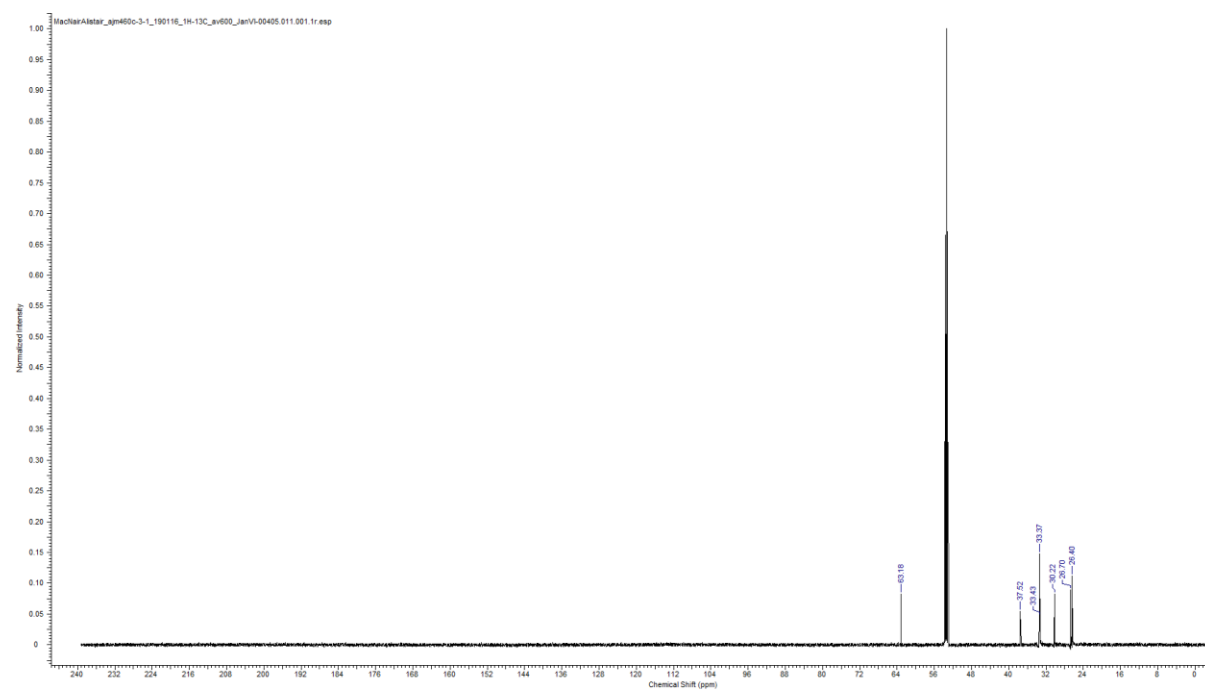
### 3-Cyclohexanepropan-1-ol (263)



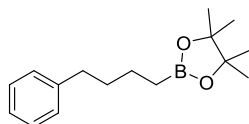
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



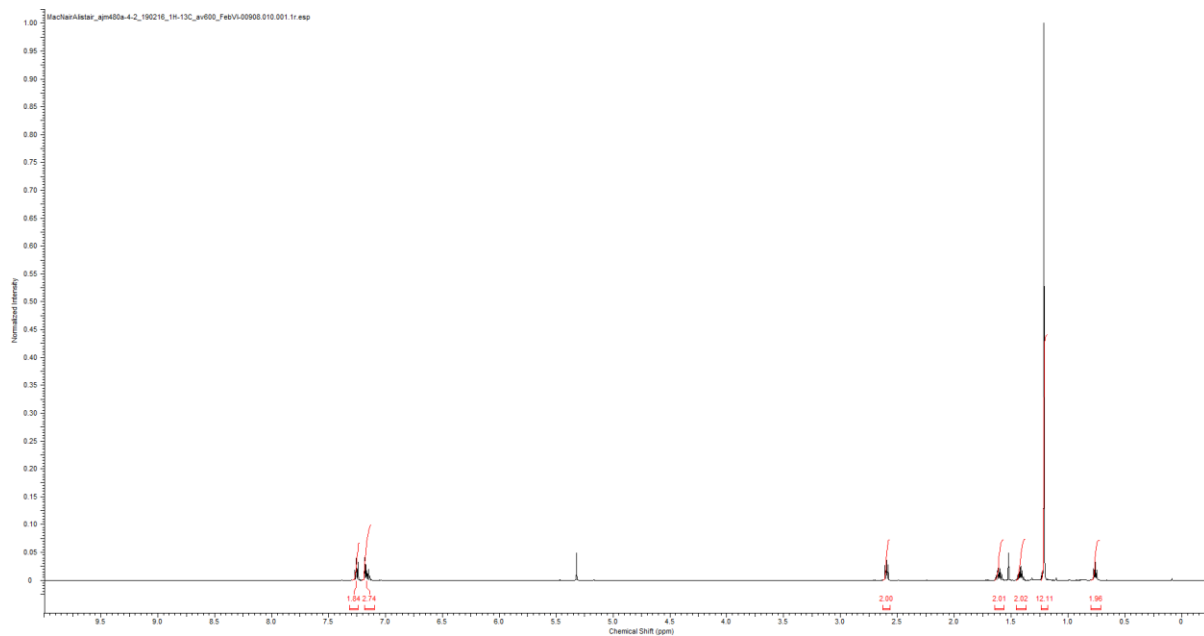
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



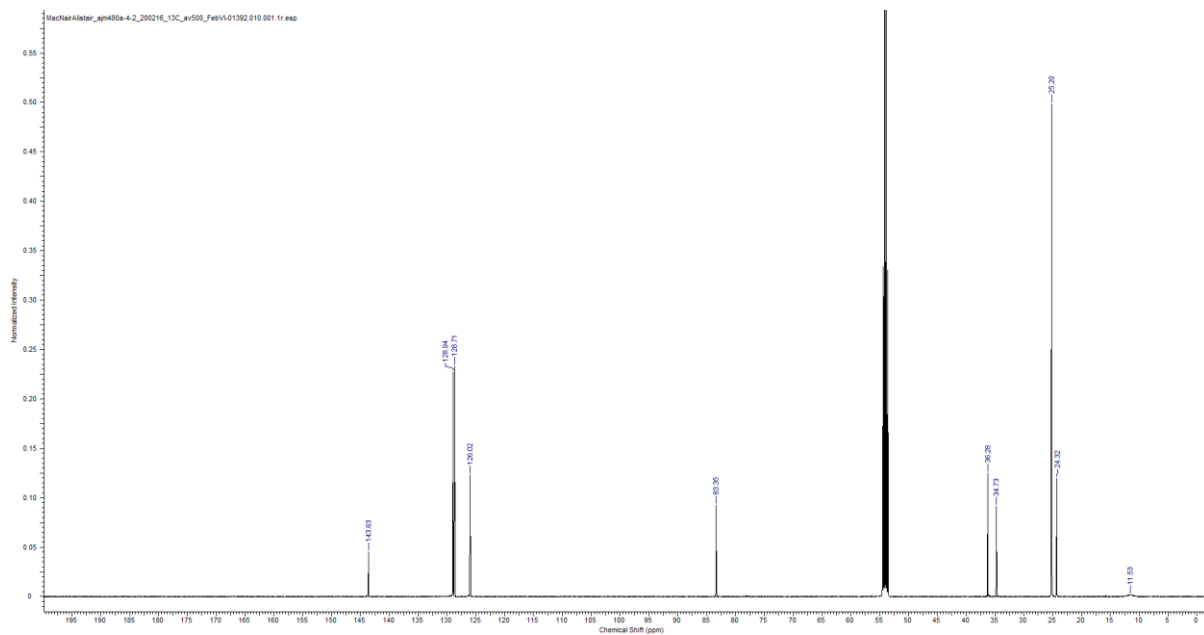
## 2-(4-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (267)



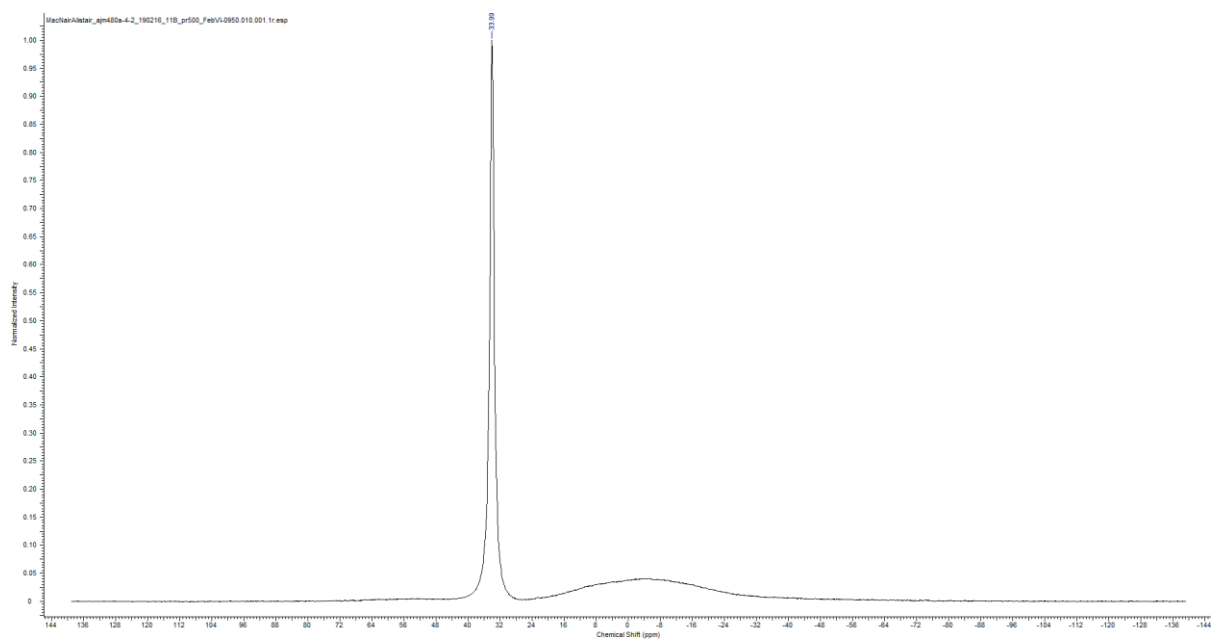
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



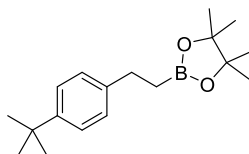
$^{13}\text{C}$ , 151 MHz,  $\text{CD}_2\text{Cl}_2$



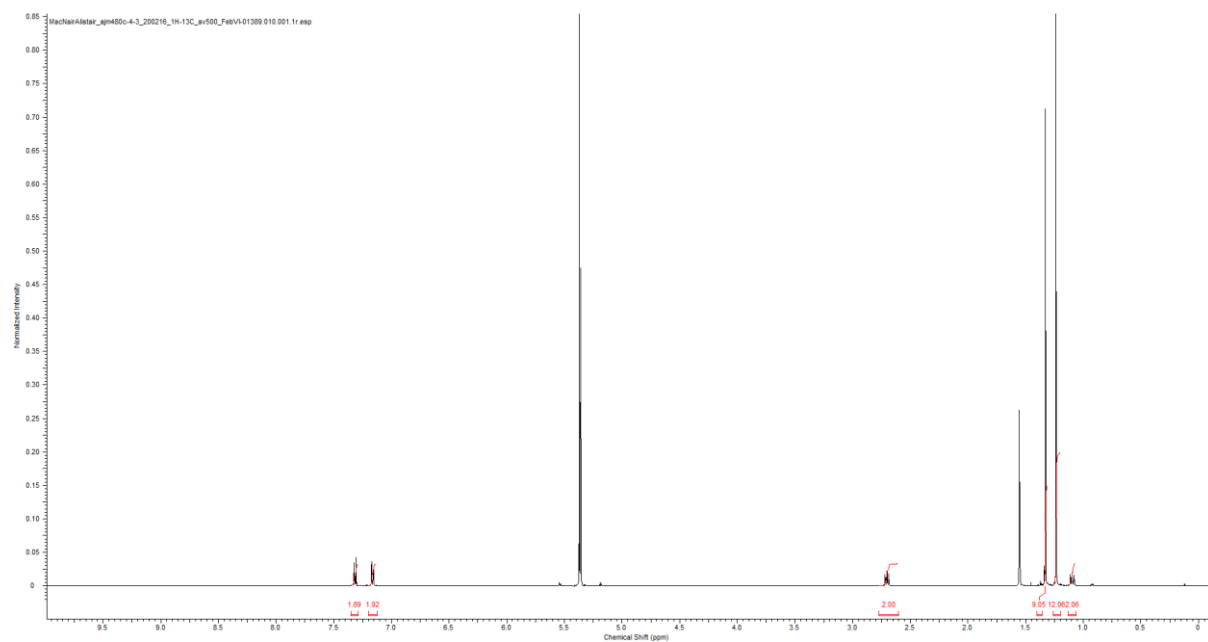
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



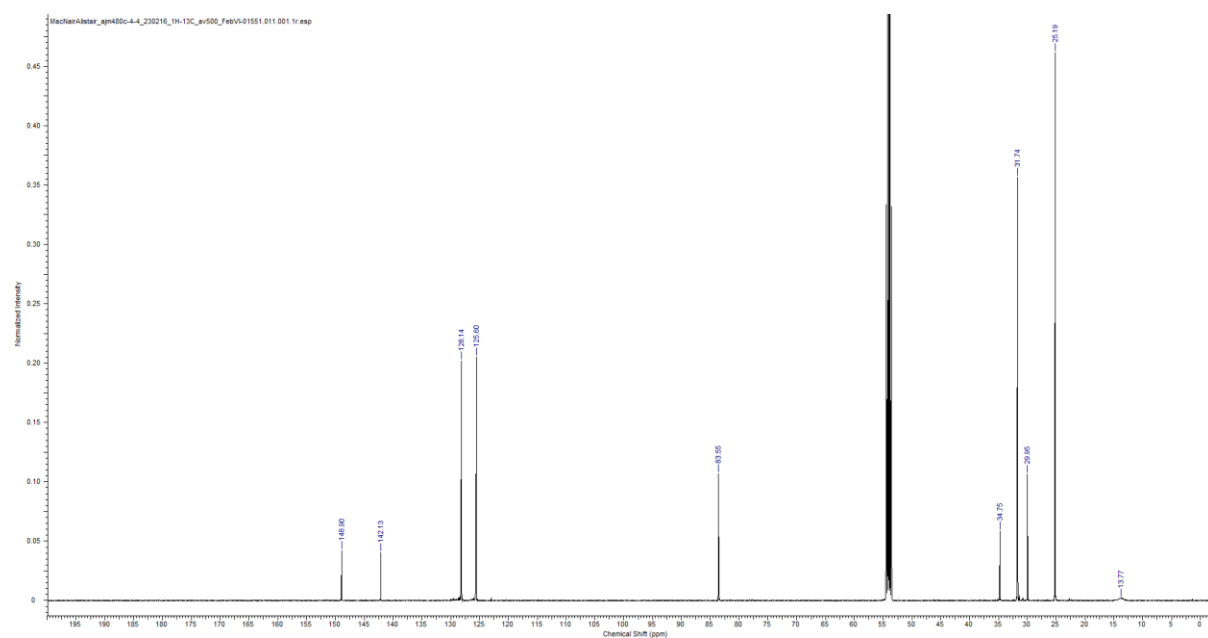
## 2-[2-(4-*tert*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (268)



$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$

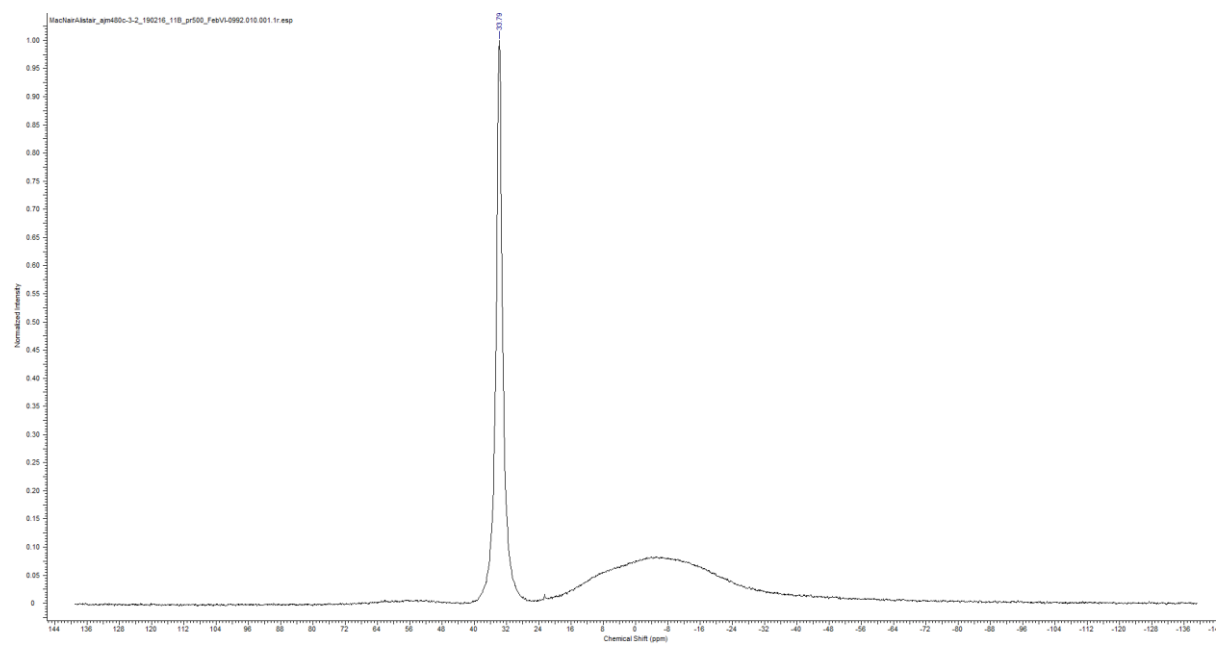


$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$

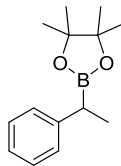




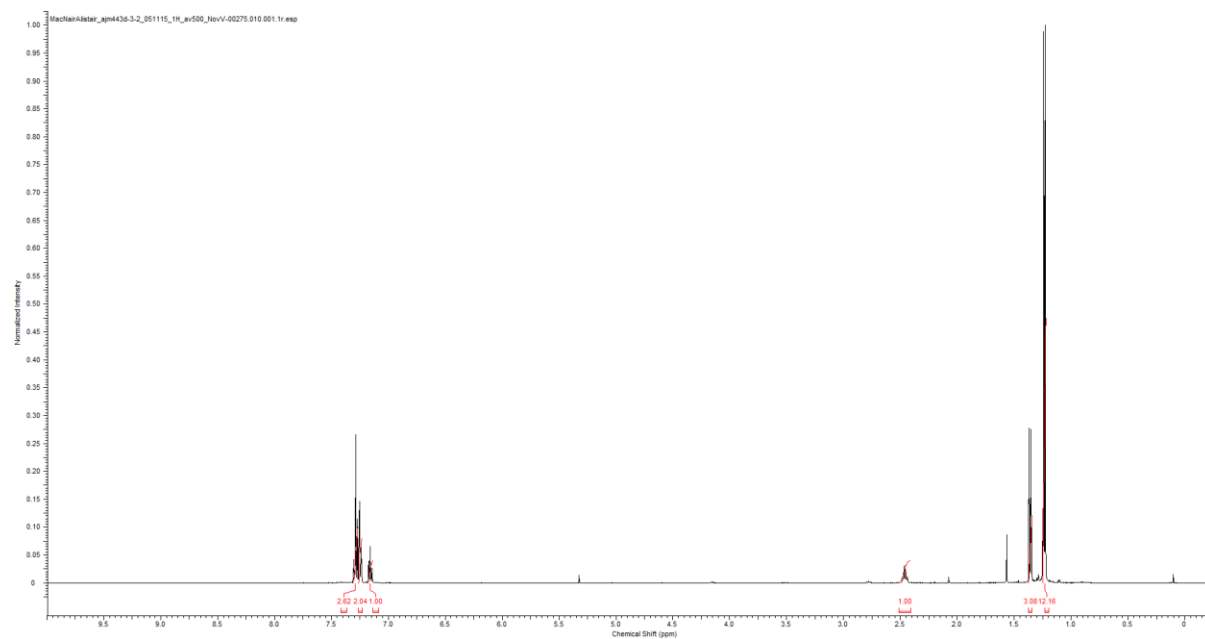
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



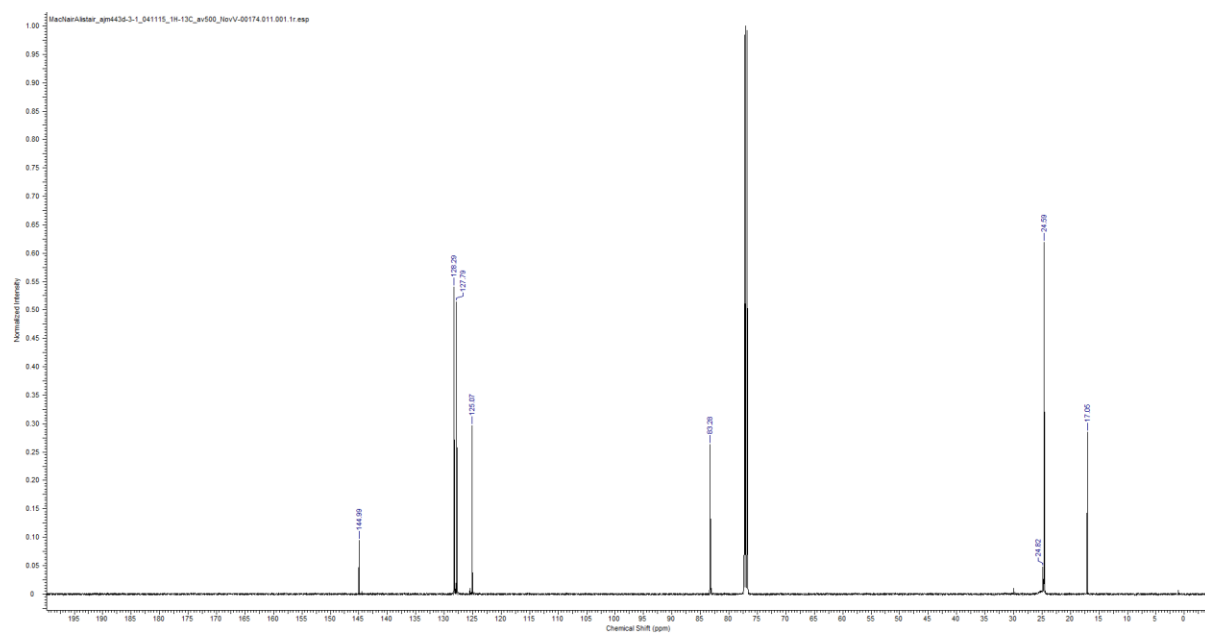
## 2-(1-Phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (194)



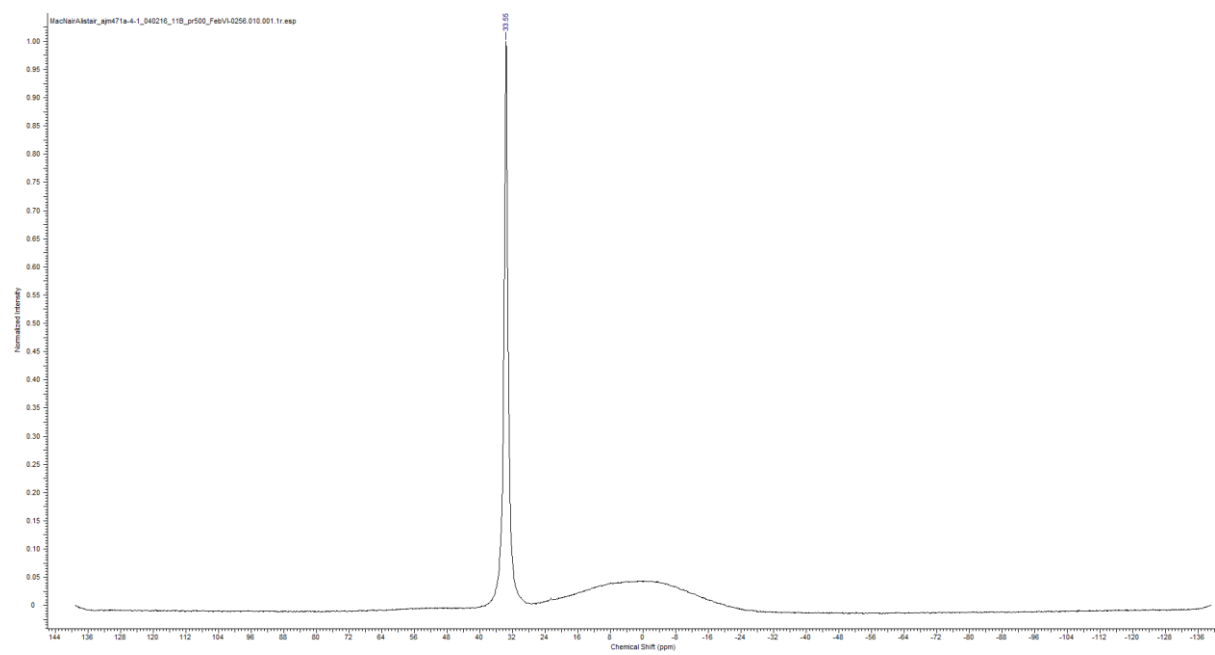
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



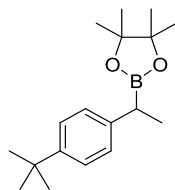
$^{13}\text{C}$ , 126 MHz,  $\text{CDCl}_3$



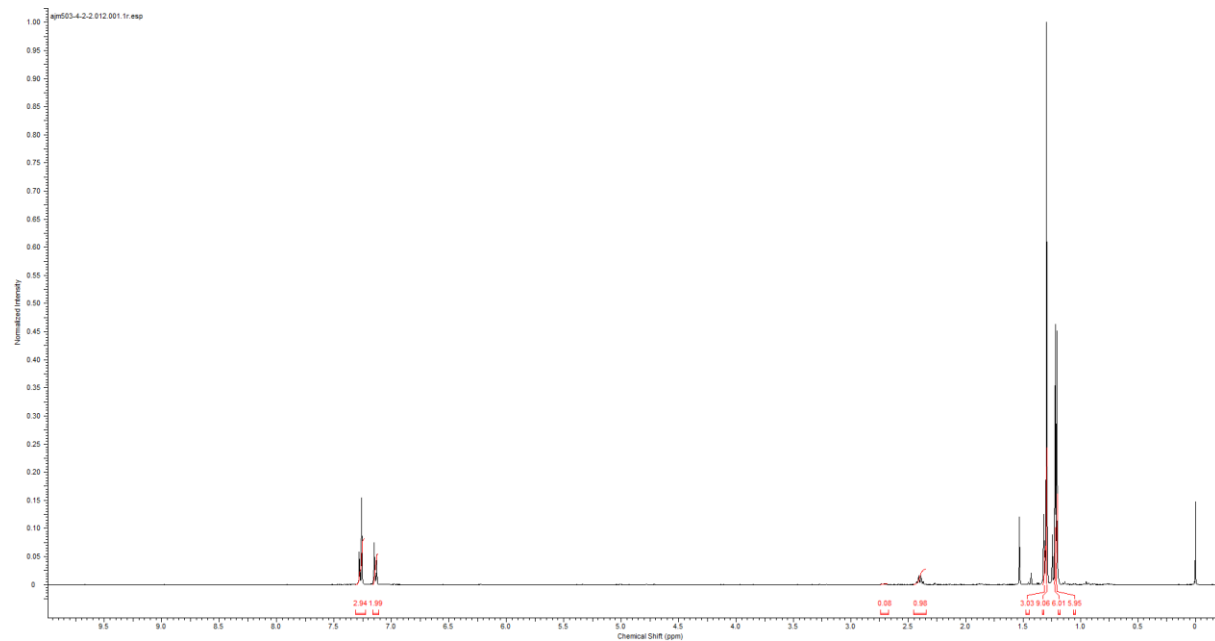
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



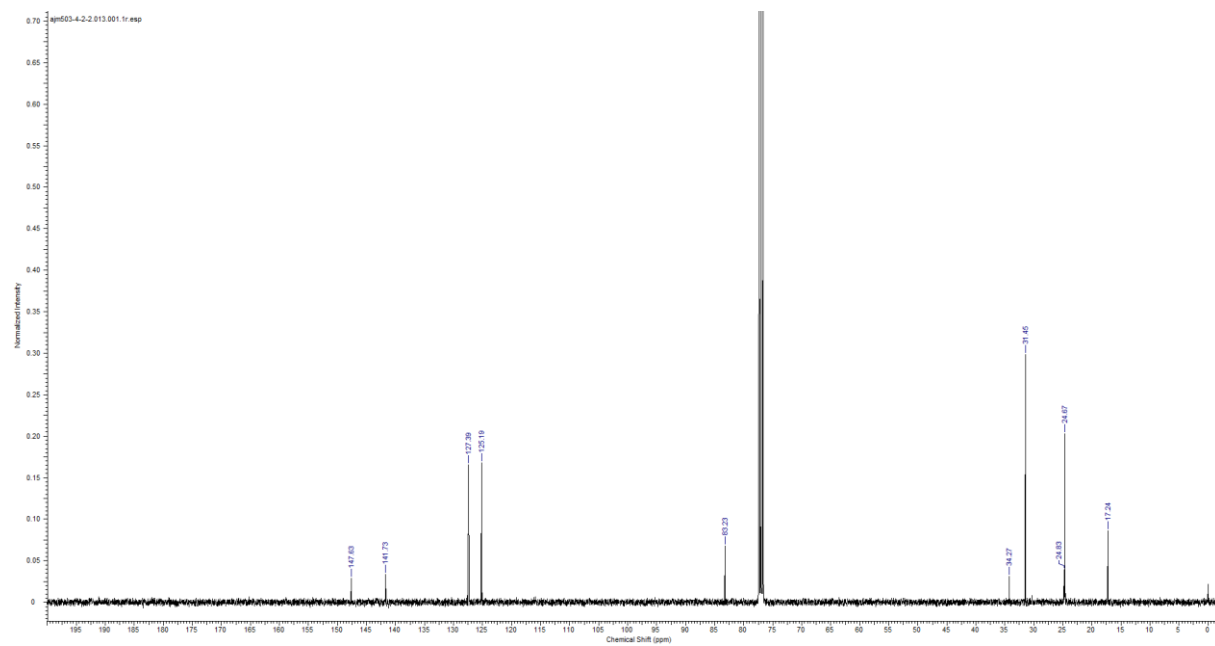
**2-[1-(4-*tert*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (271)**



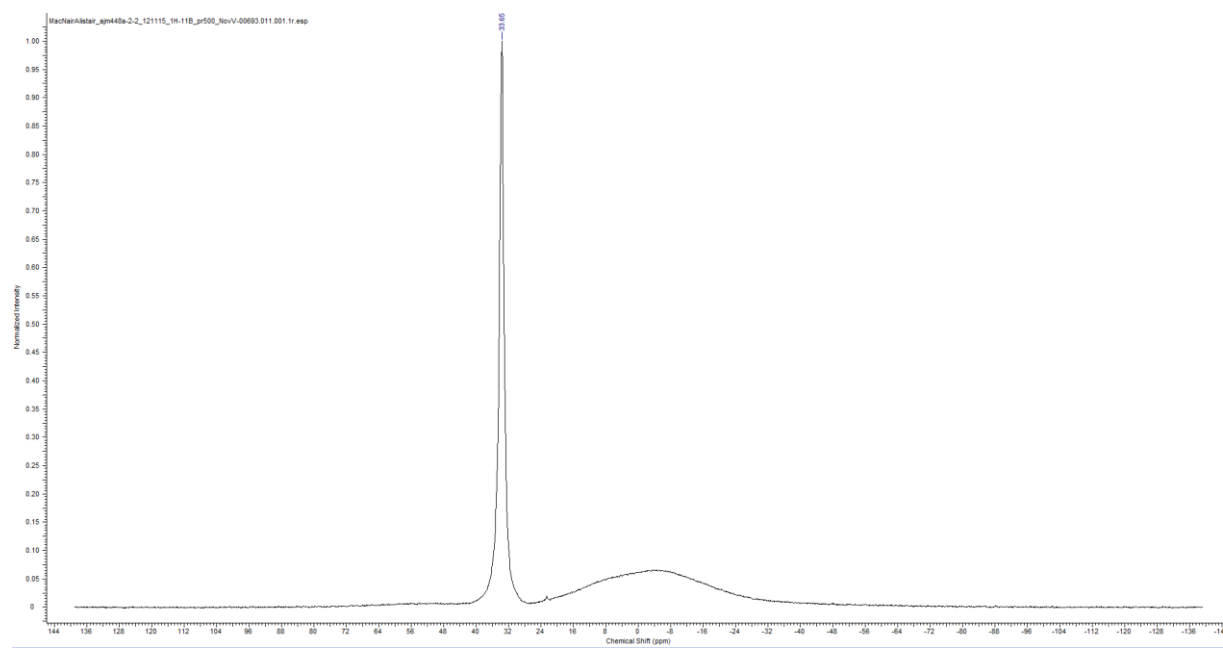
$^1\text{H}$ , 500 MHz,  $\text{CDCl}_3$



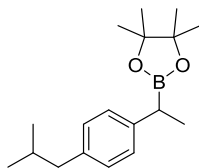
$^{13}\text{C}$ , 100 MHz,  $\text{CDCl}_3$



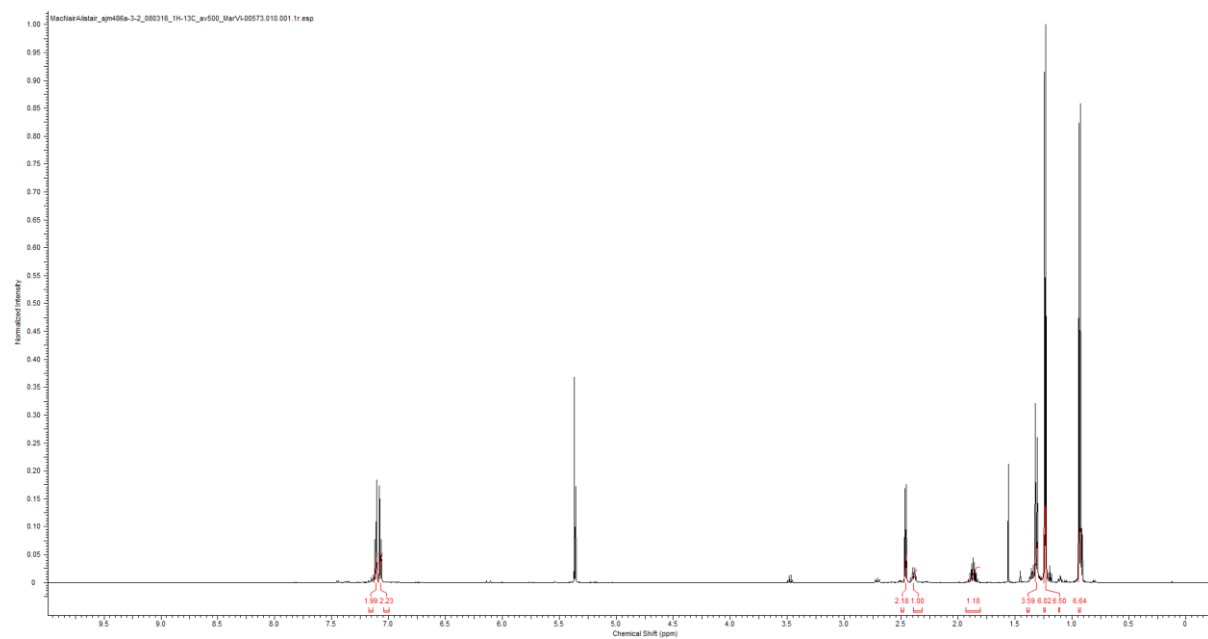
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



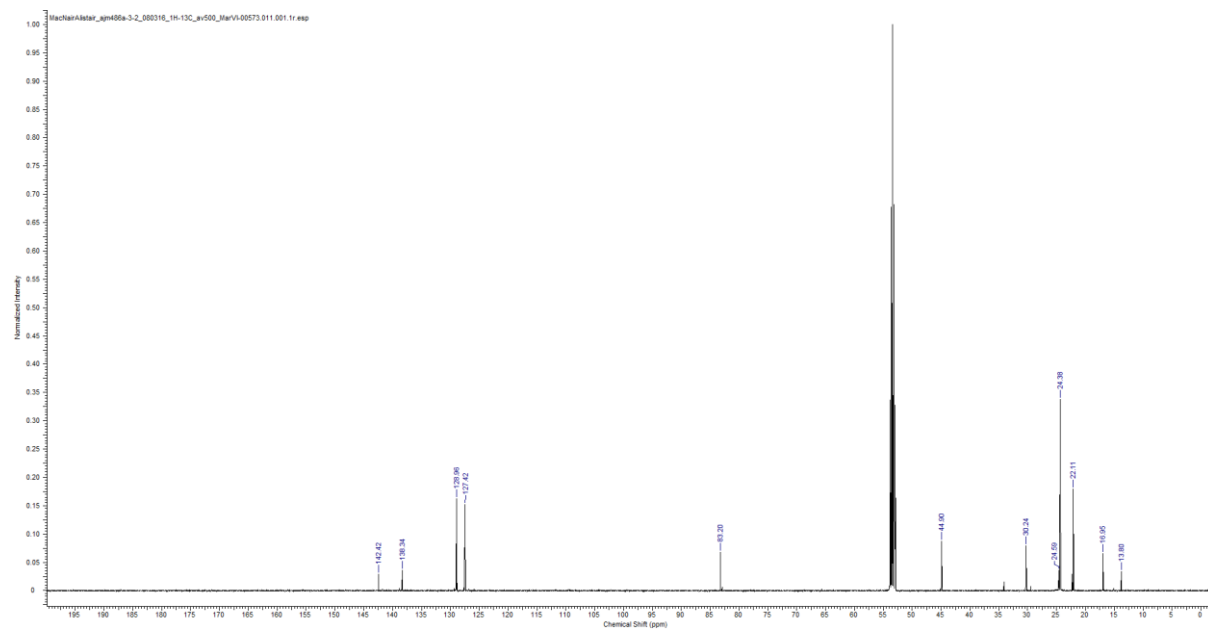
## 2-[1-(4-*iso*-Butylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (272)



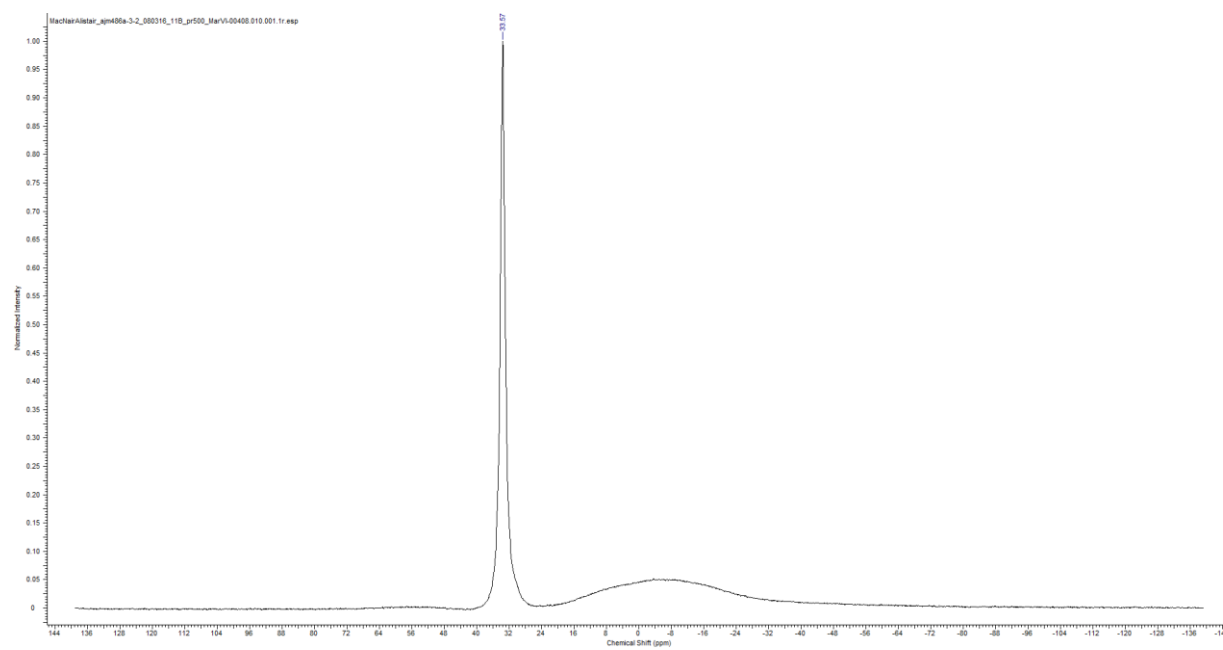
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



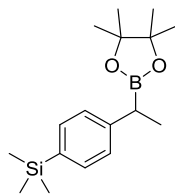
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



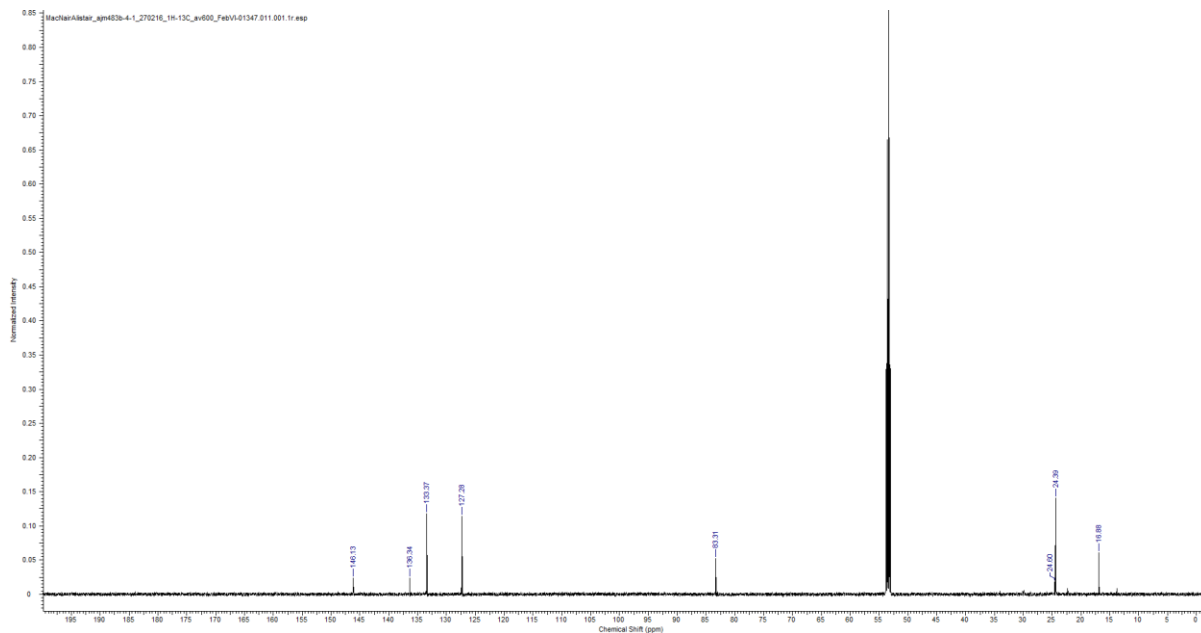
## 2-[1-(4-Trimethylsilylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (273)



$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$

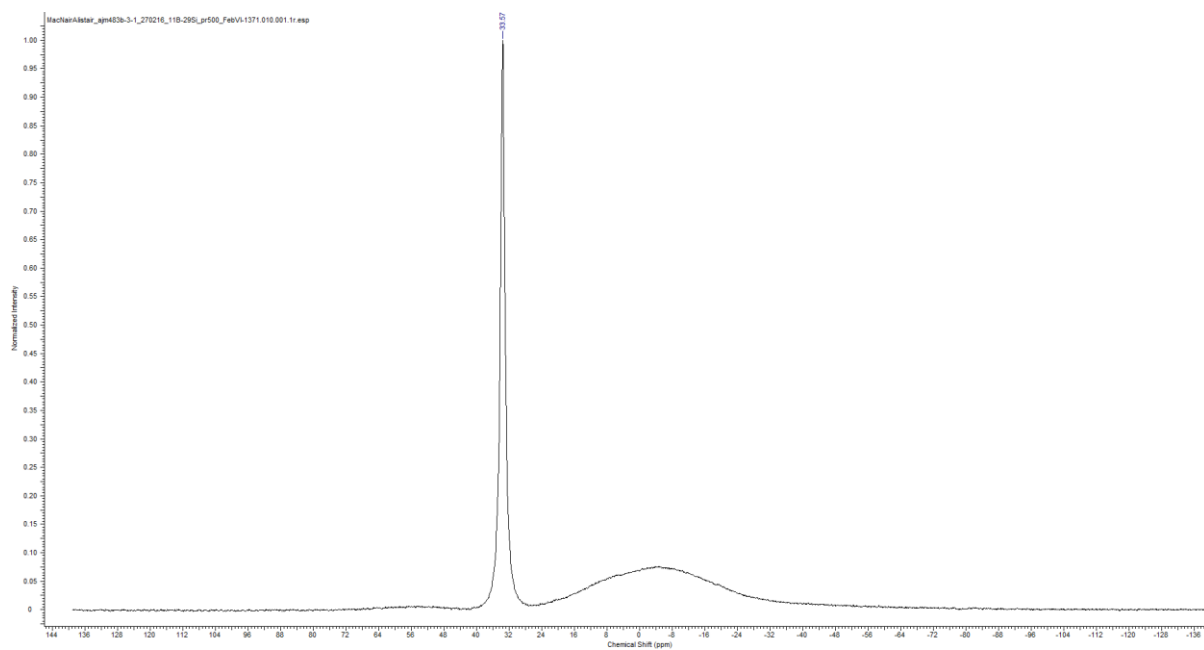


$^{13}\text{C}$ , 151 MHz,  $\text{CD}_2\text{Cl}_2$

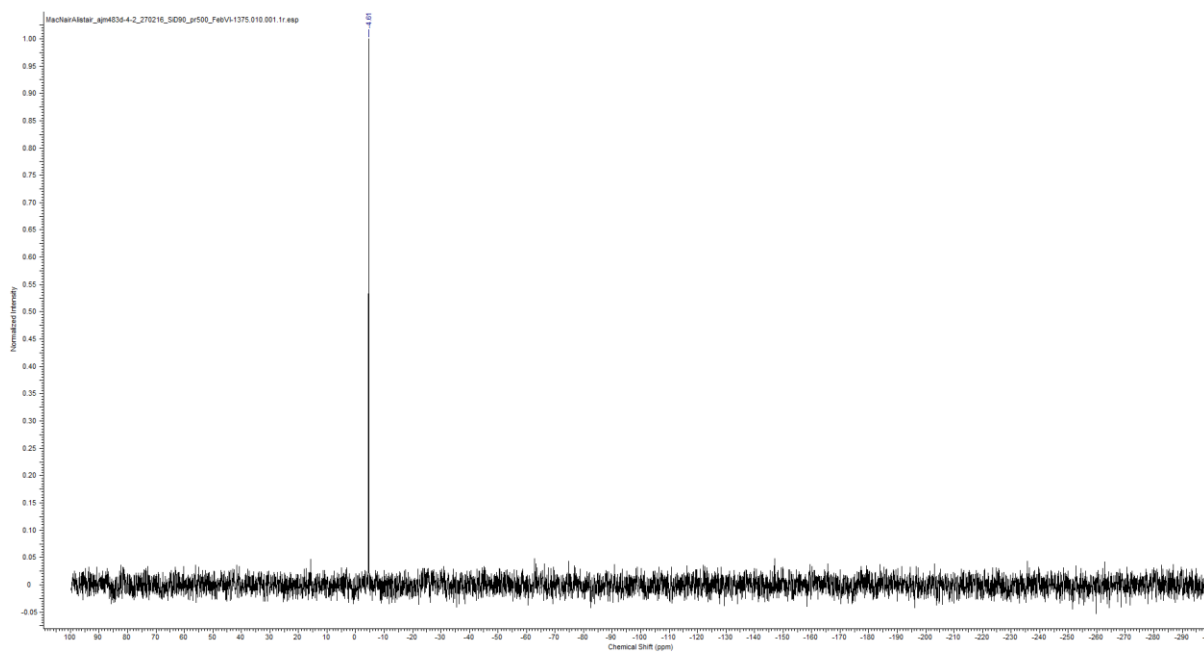




$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$

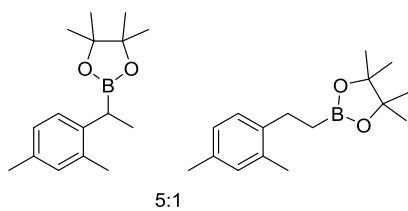


$^{29}\text{Si}$ , 99 MHz,  $\text{CD}_2\text{Cl}_2$

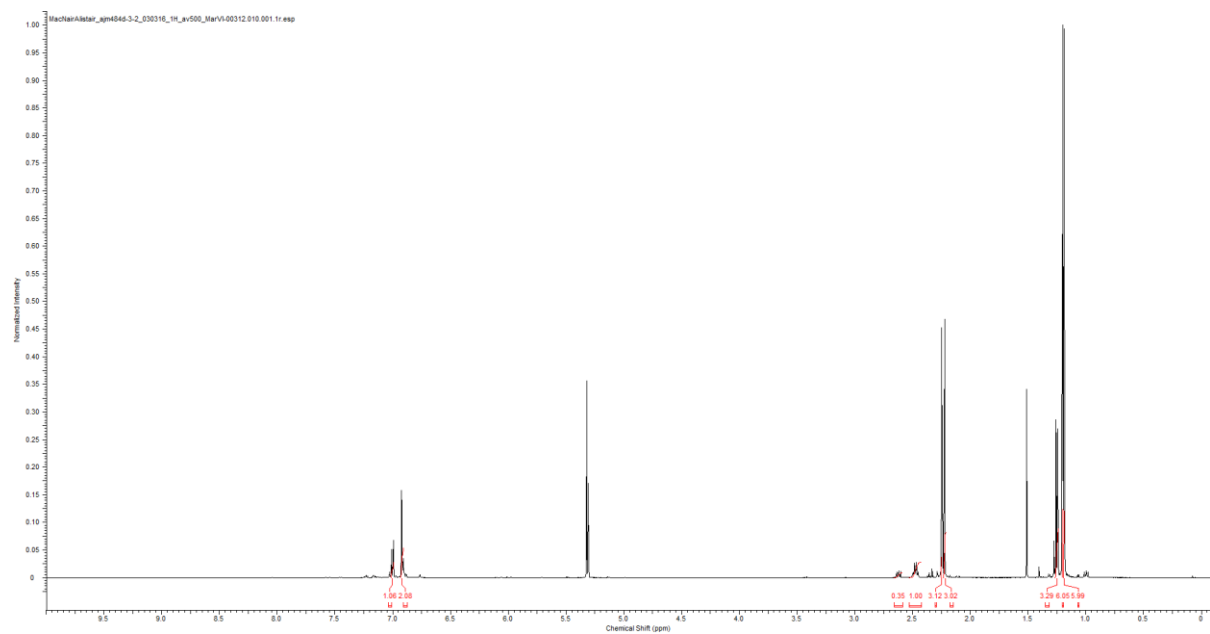


## 2-[1-(2,4-Dimethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (272)

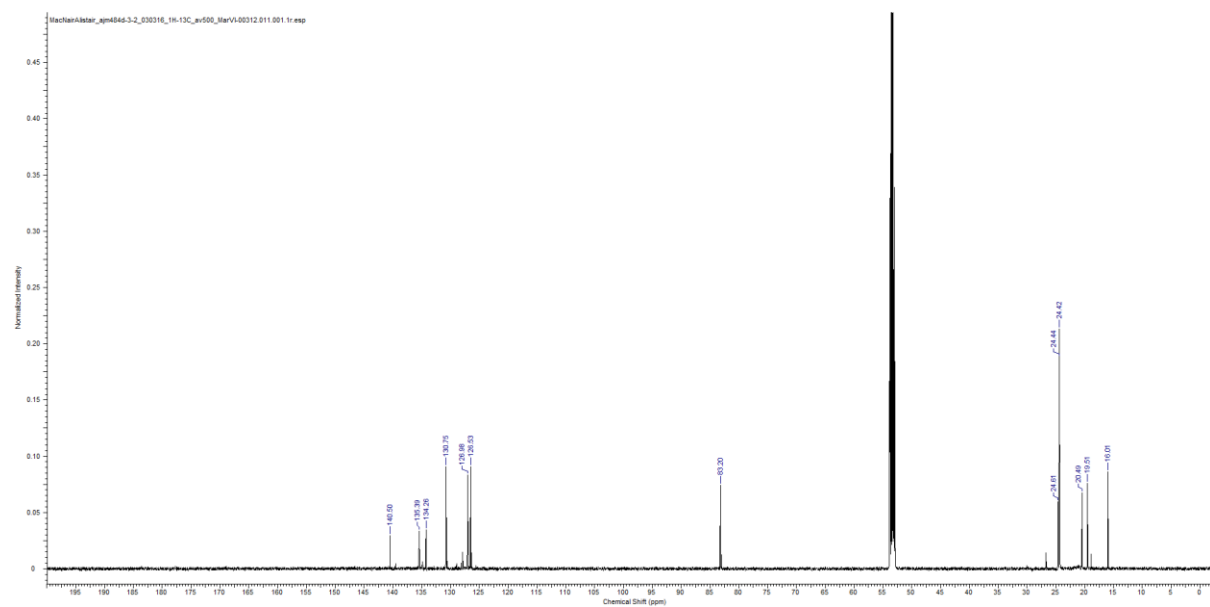
Isolated as a 5:1 mixture with the linear isomer



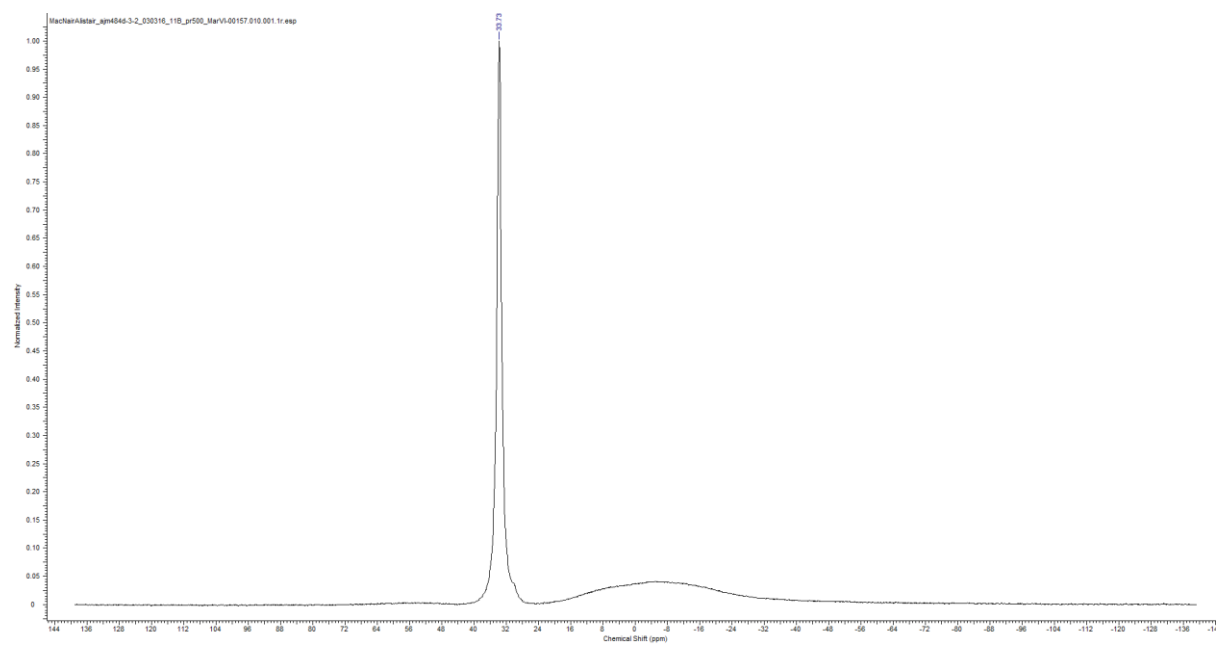
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



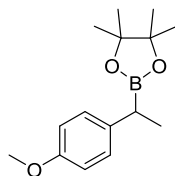
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



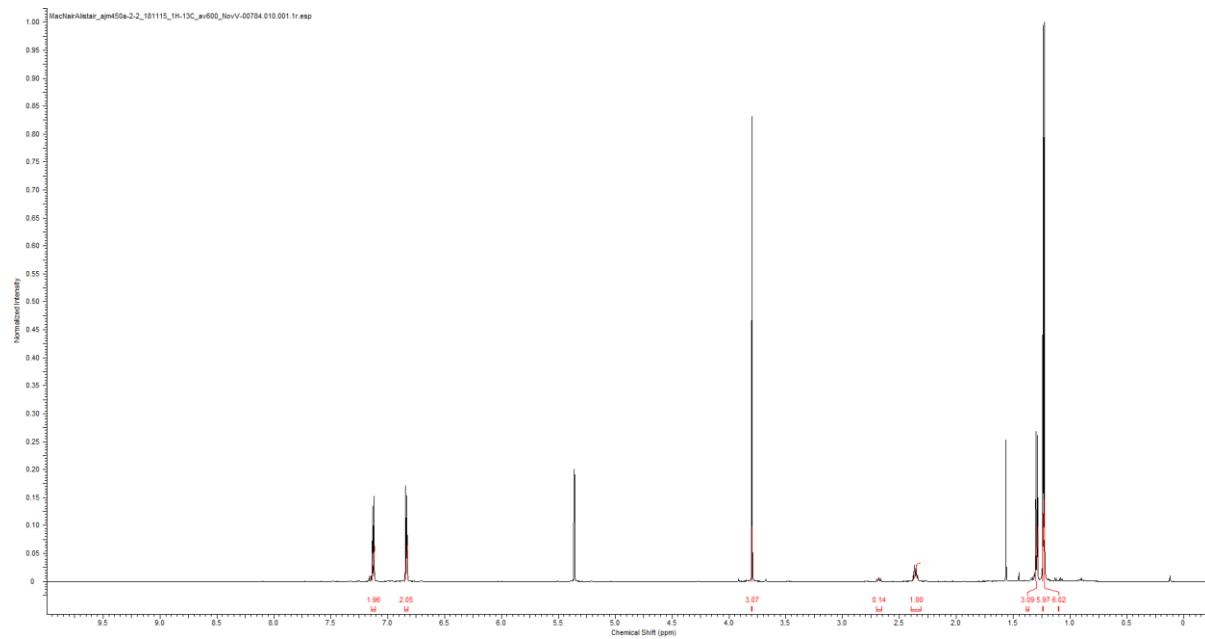
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



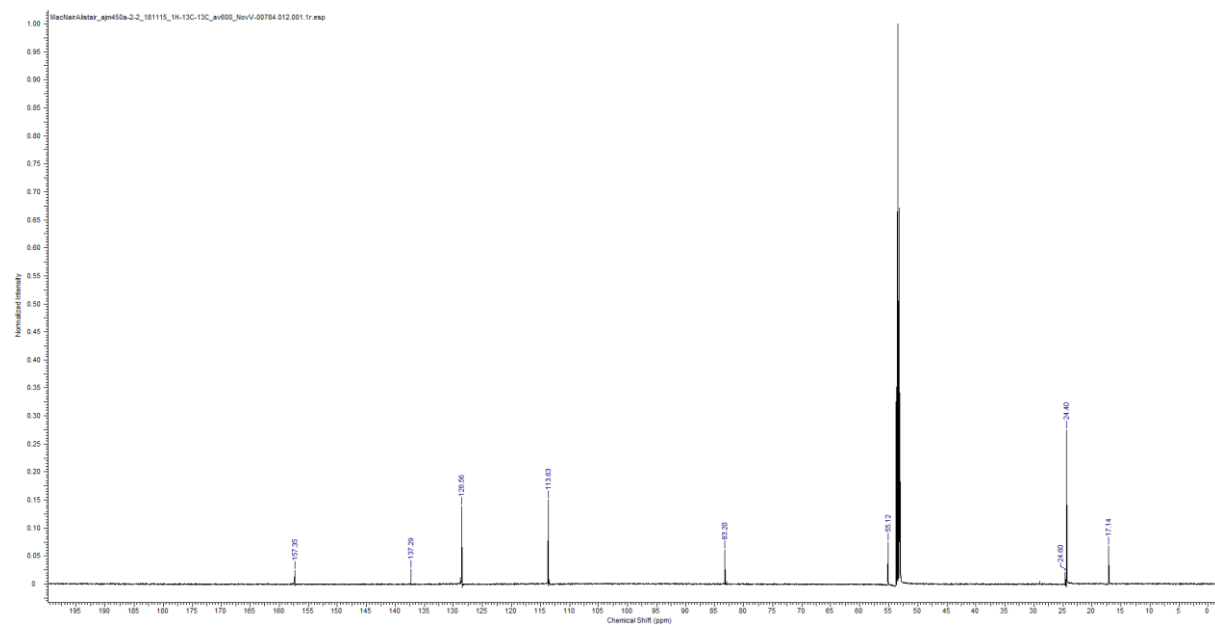
## 2-[1-(4-Methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (277)



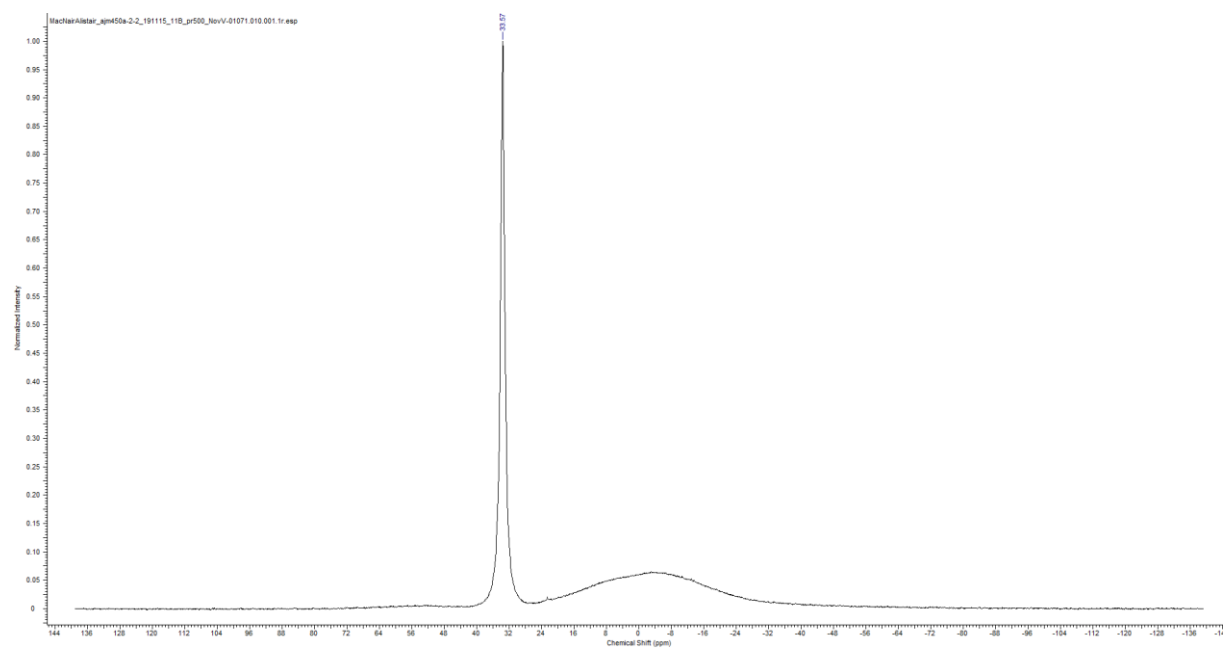
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



$^{13}\text{C}$ , 151 MHz,  $\text{CD}_2\text{Cl}_2$

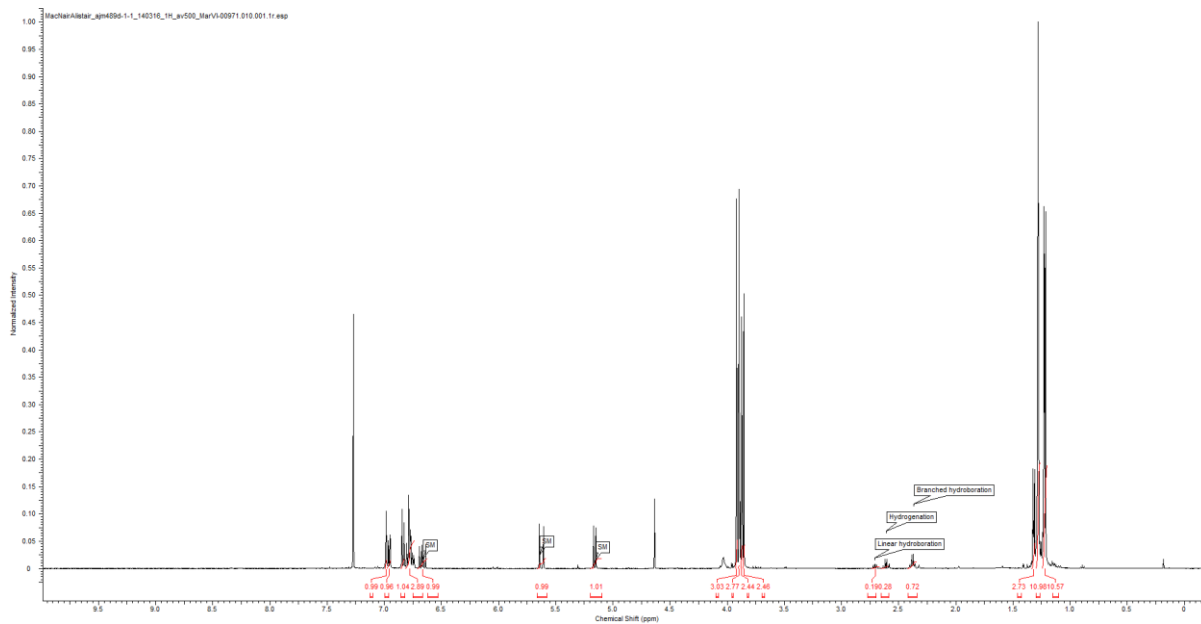
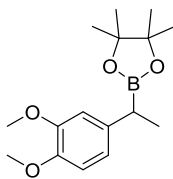


$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$

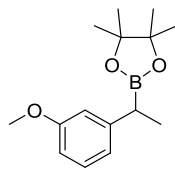


## 2-[1-(3,4-Dimethoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (278)

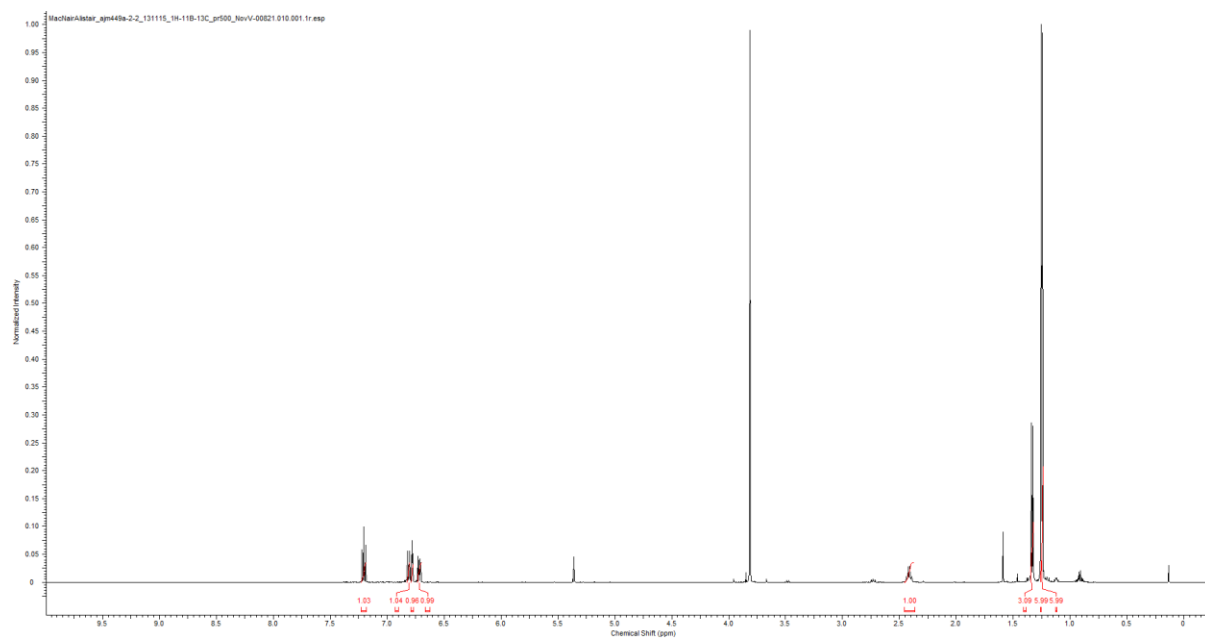
Product decomposed during flash column chromatography. NMR of crude product mixture shown.



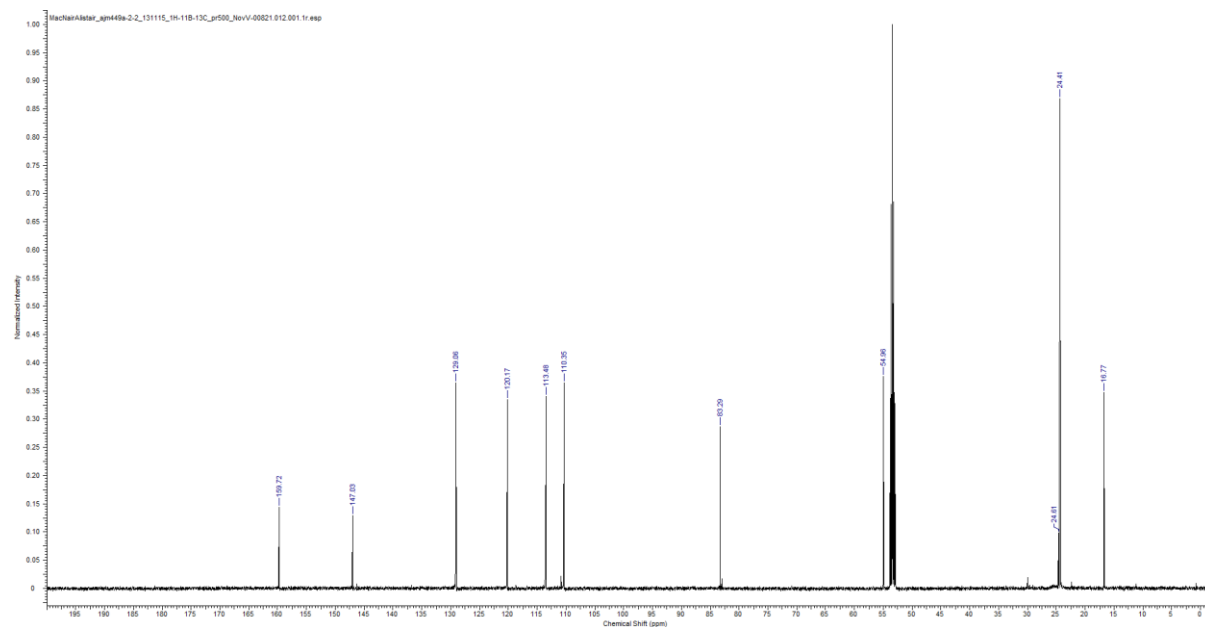
## 2-[1-(3-Methoxy phenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (279)



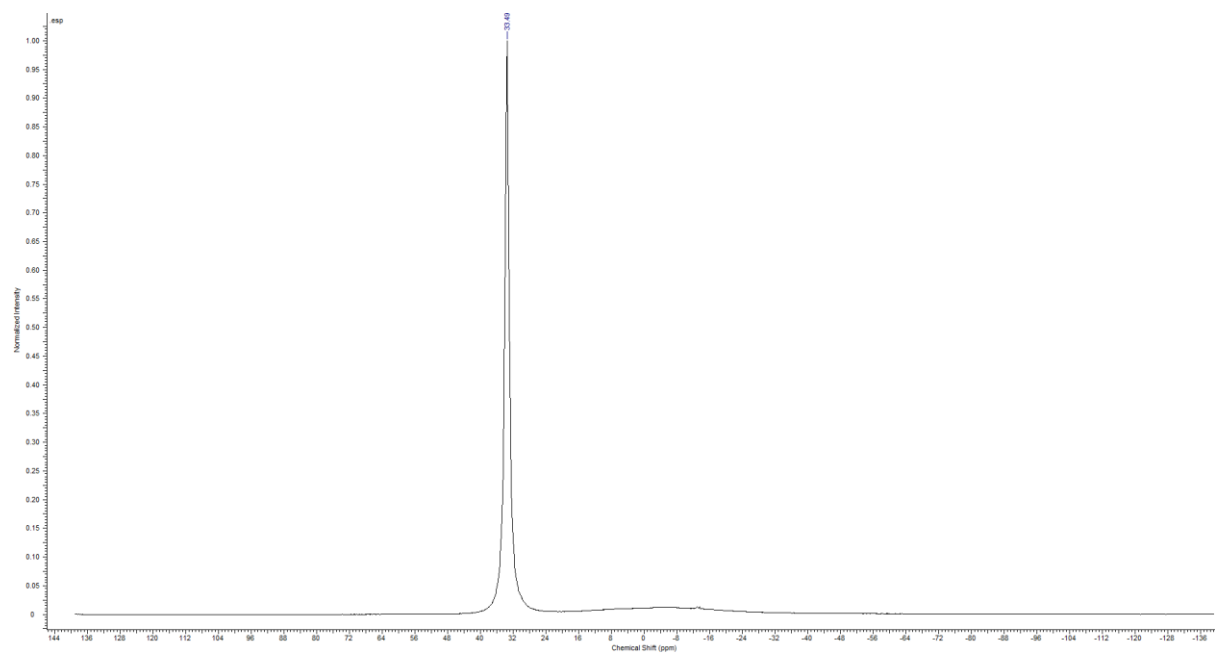
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$

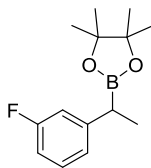


$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$

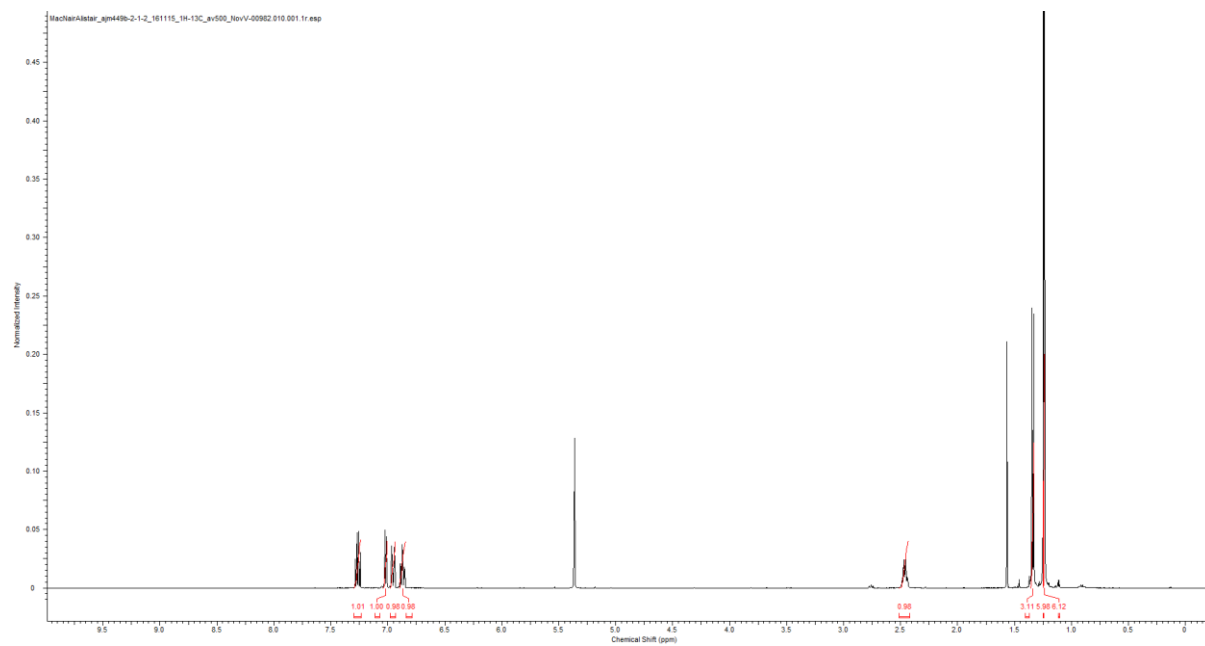




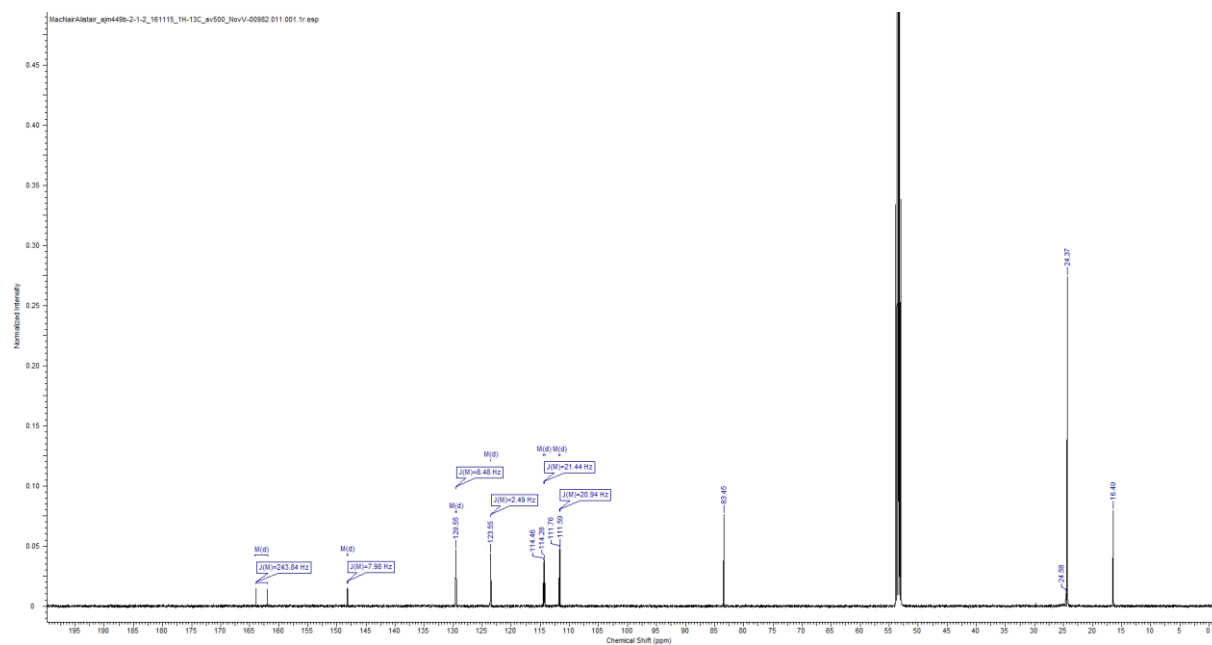
## 2-[1-(3-Fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (283)



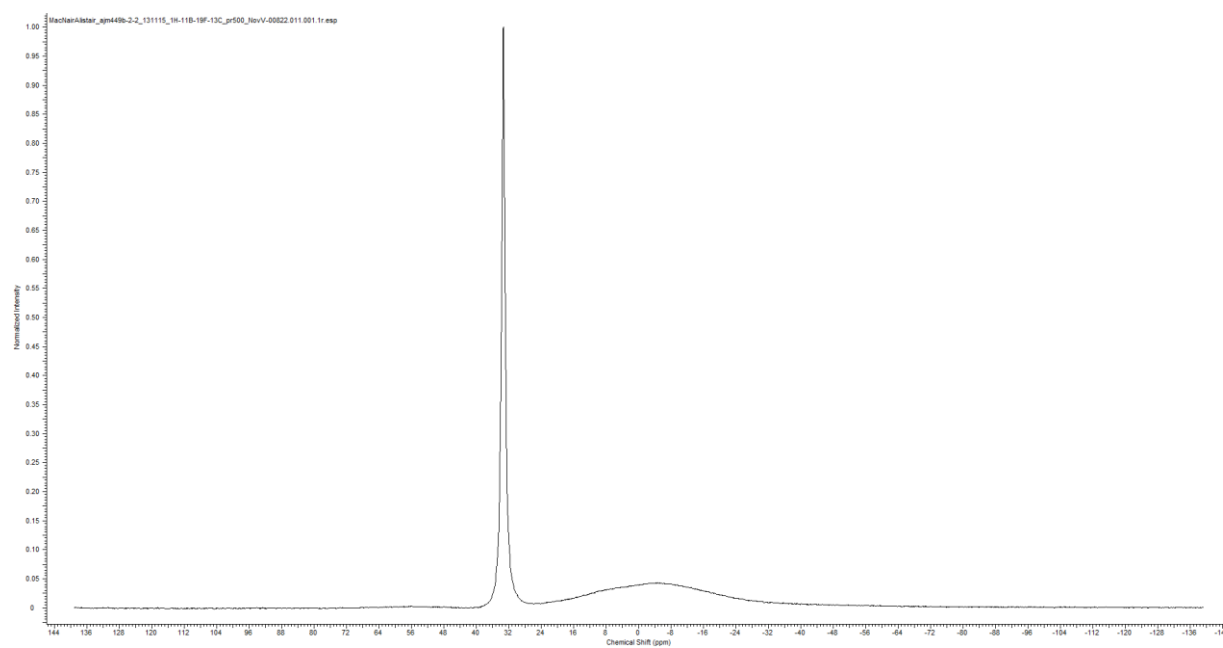
$^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$



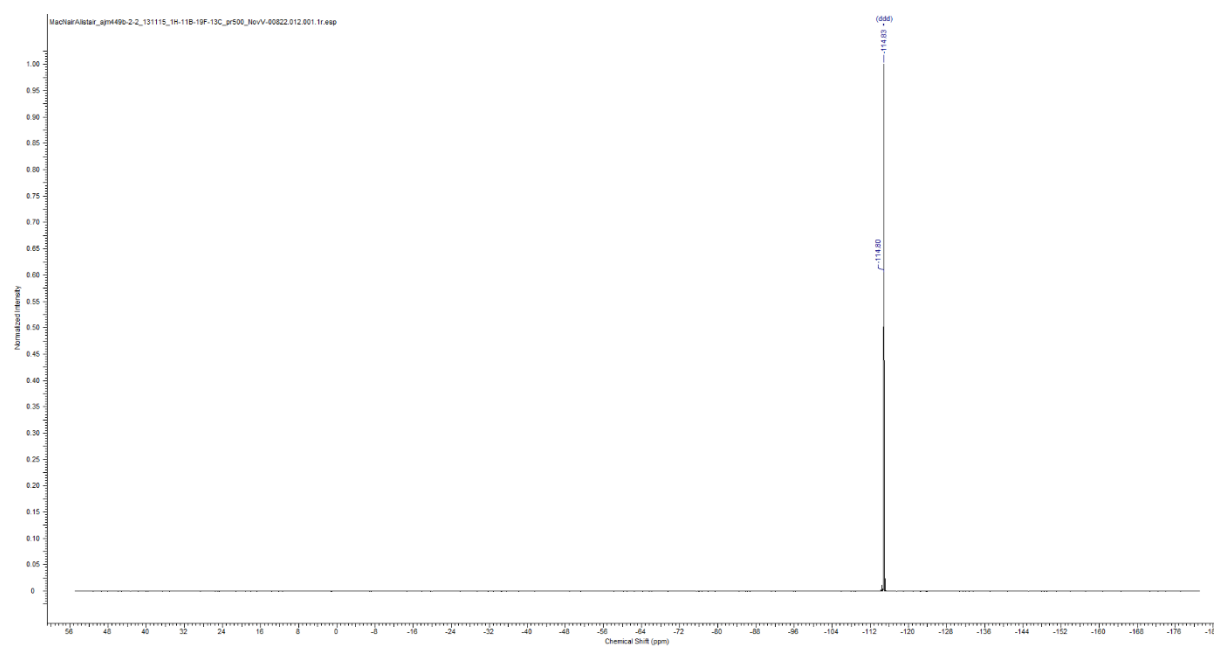
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



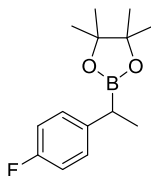
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



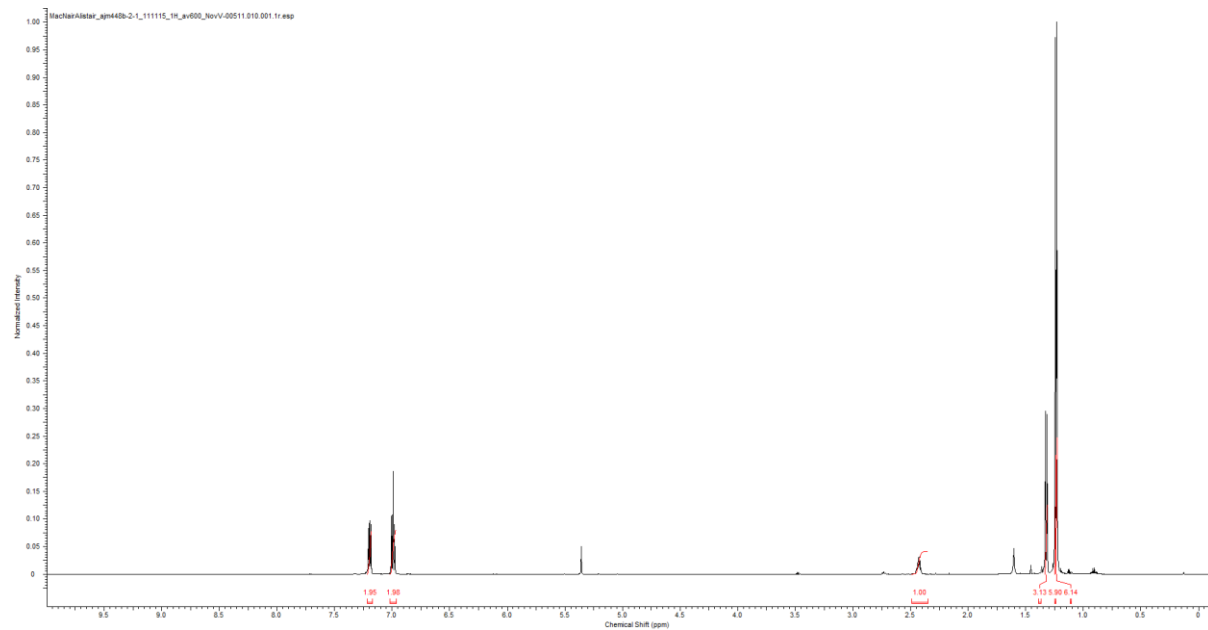
$^{19}\text{F}$ , 471 MHz,  $\text{CD}_2\text{Cl}_2$



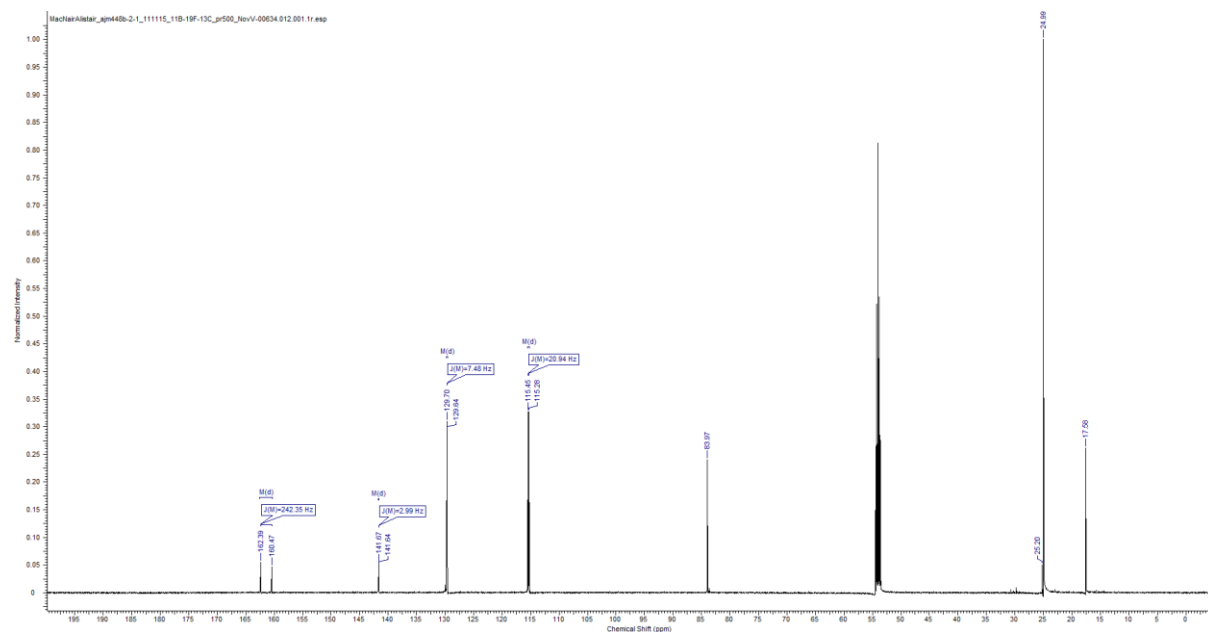
## 2-[1-(4-Fluorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (284)



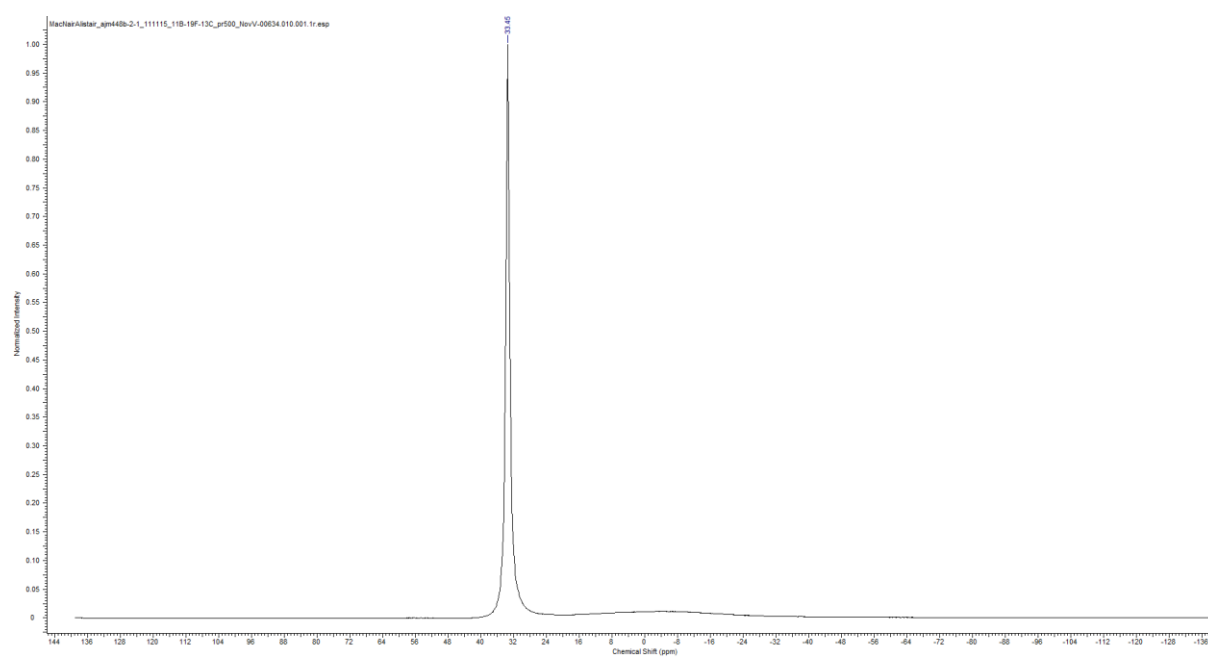
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



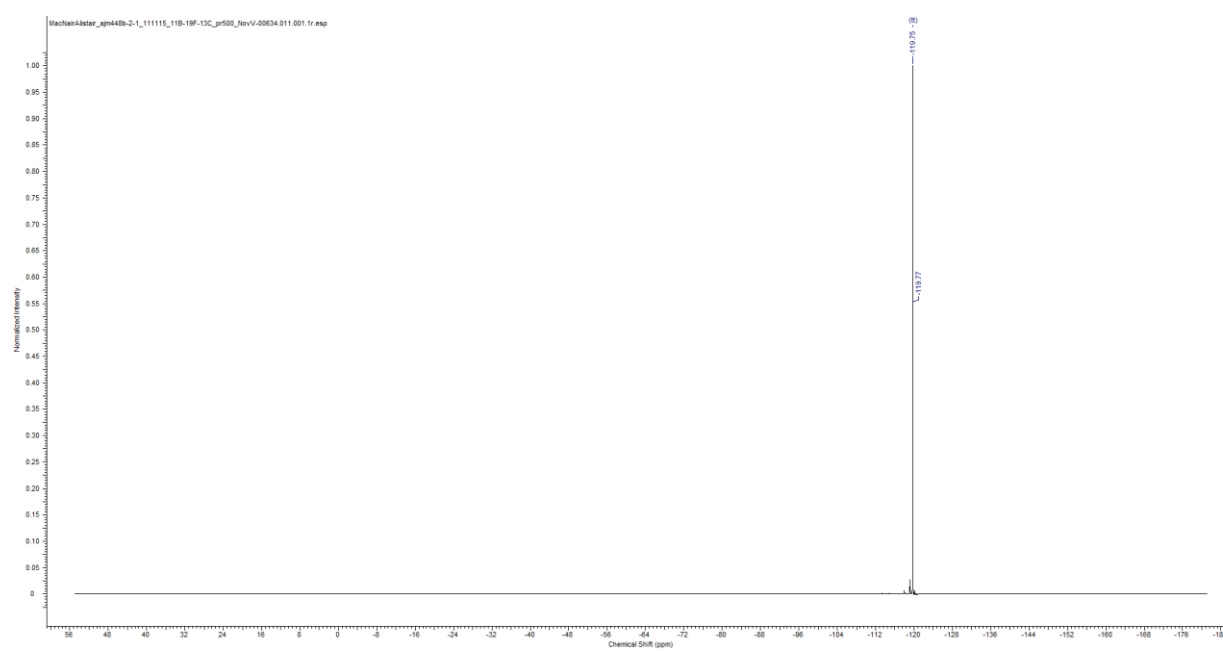
$^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$



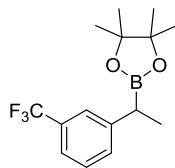
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



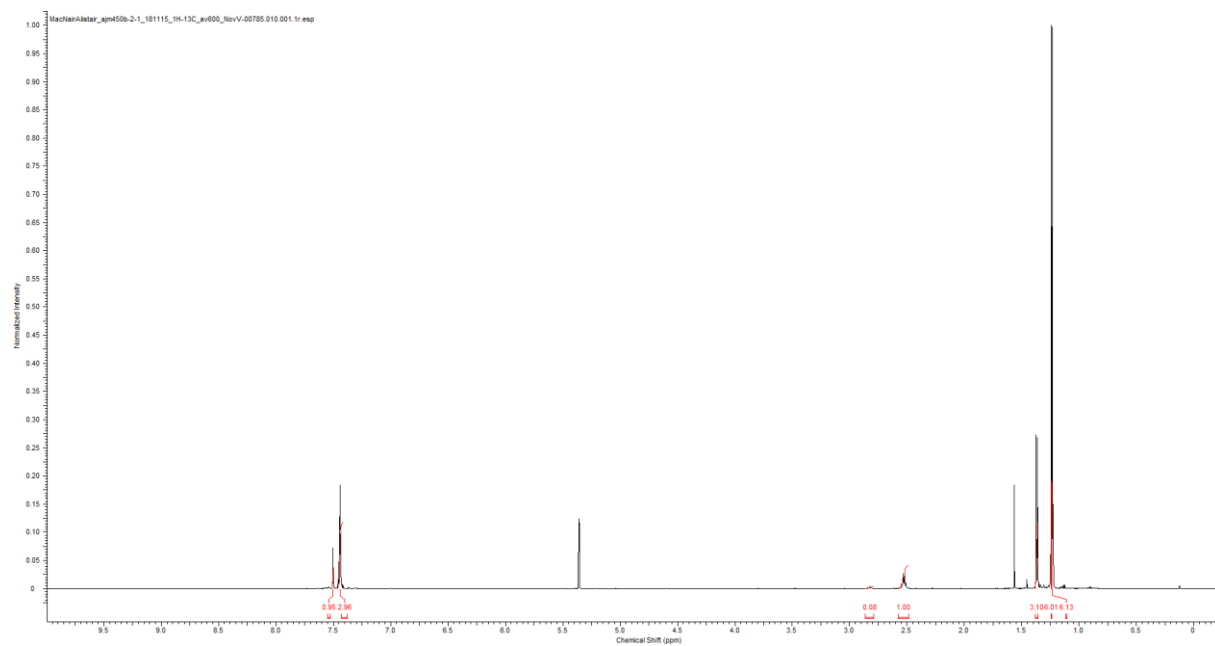
$^{19}\text{F}$ , 471 MHz,  $\text{CD}_2\text{Cl}_2$



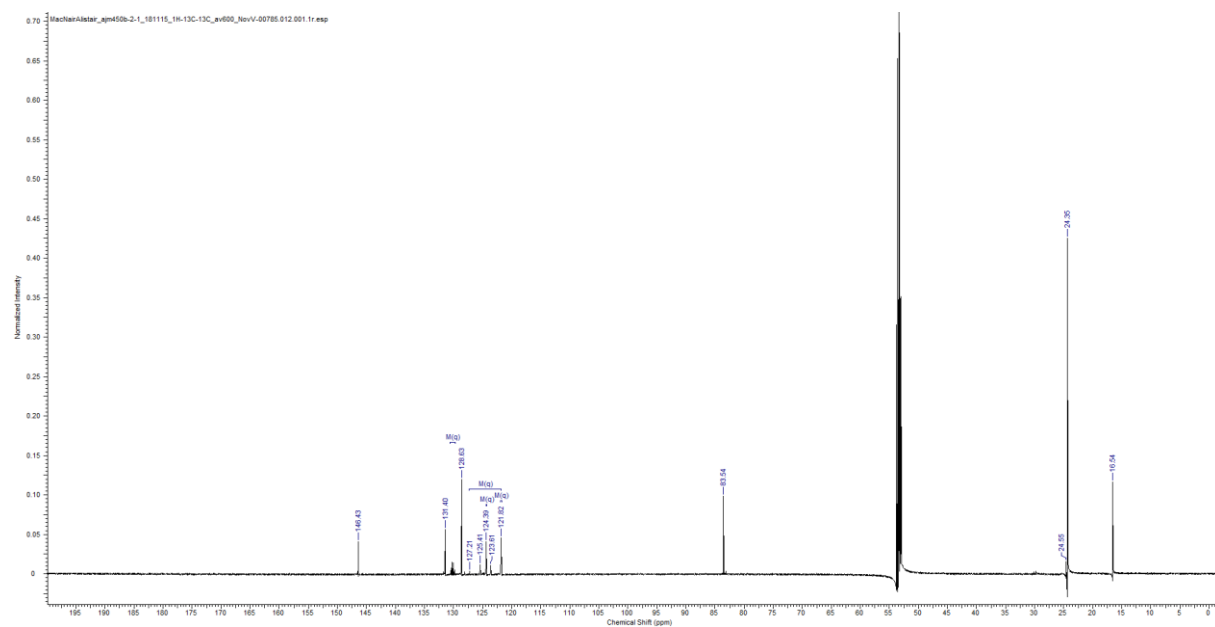
## 2-[1-(3-Trifluoromethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (285)



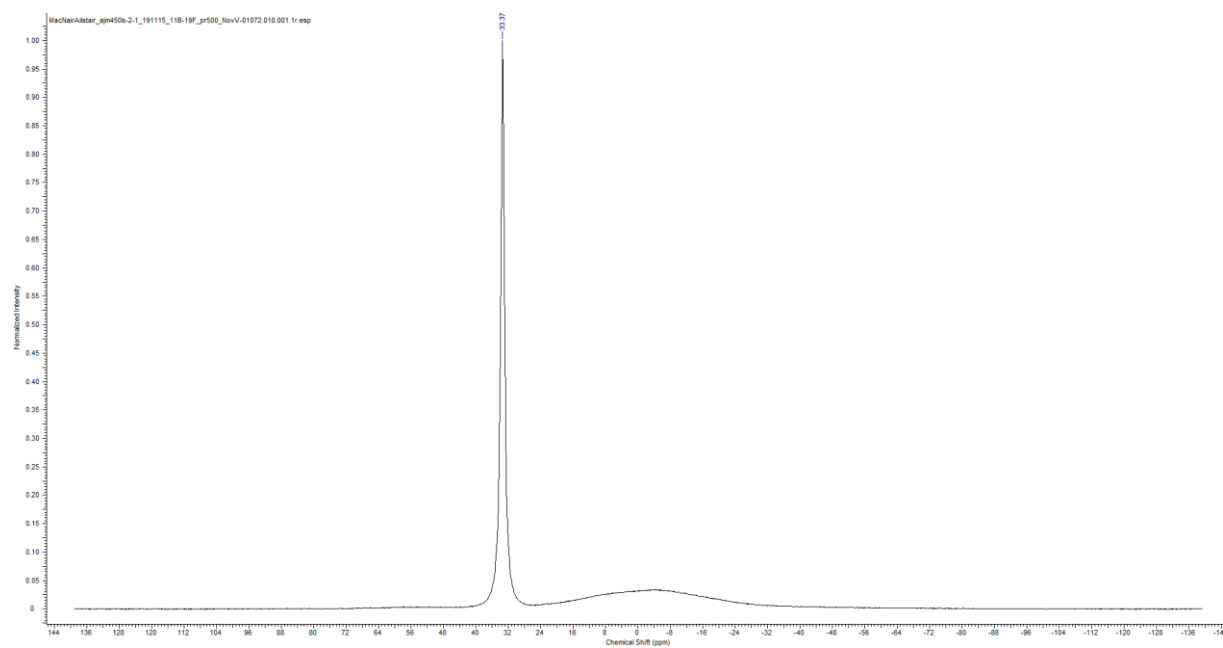
$^1\text{H}$ , 600 MHz,  $\text{CD}_2\text{Cl}_2$



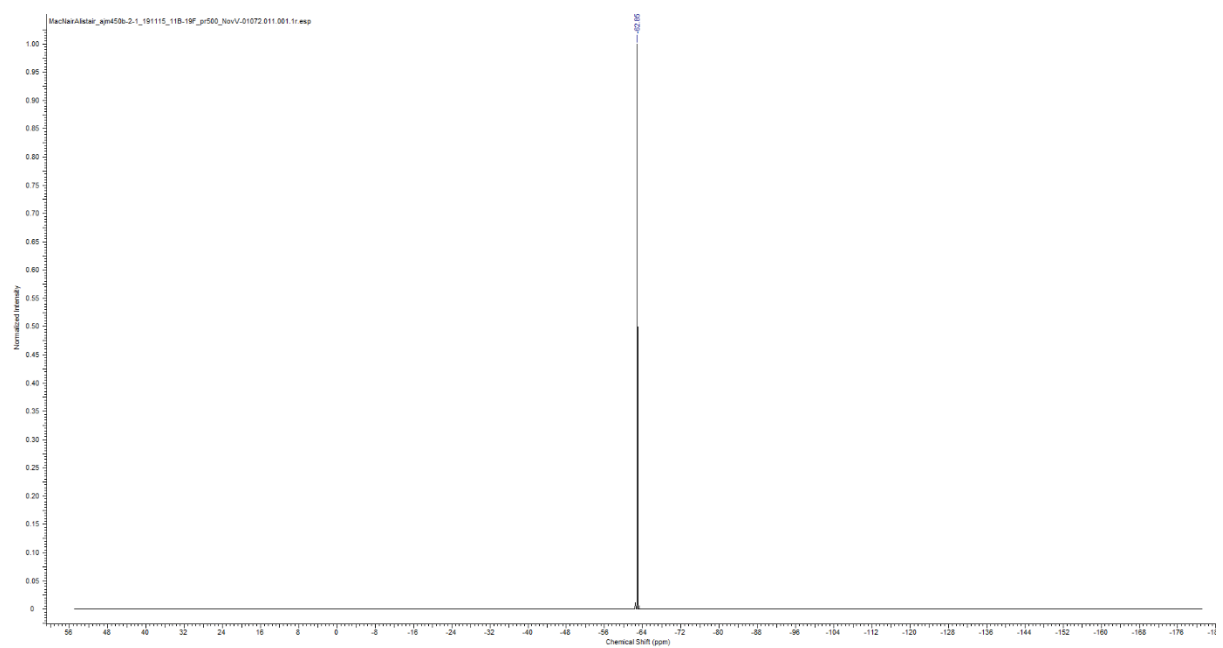
$^{13}\text{C}$ , 151 MHz,  $\text{CD}_2\text{Cl}_2$



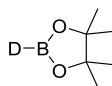
$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



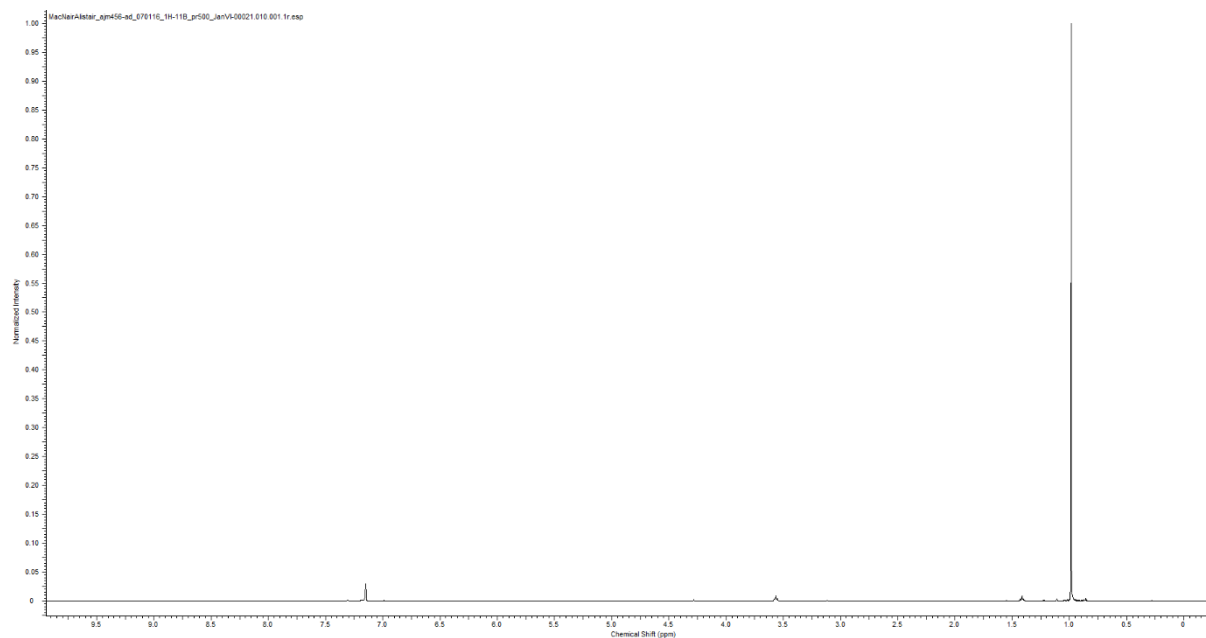
$^{19}\text{F}$ , 471 MHz,  $\text{CD}_2\text{Cl}_2$



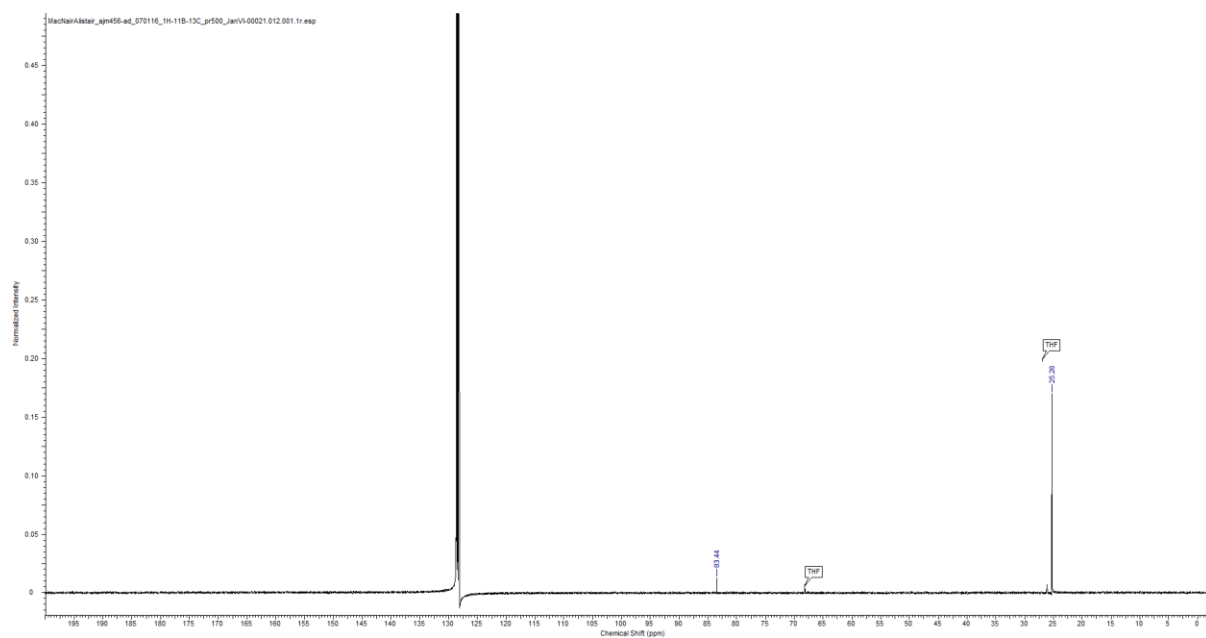
## $d_1$ -Pinacolborane

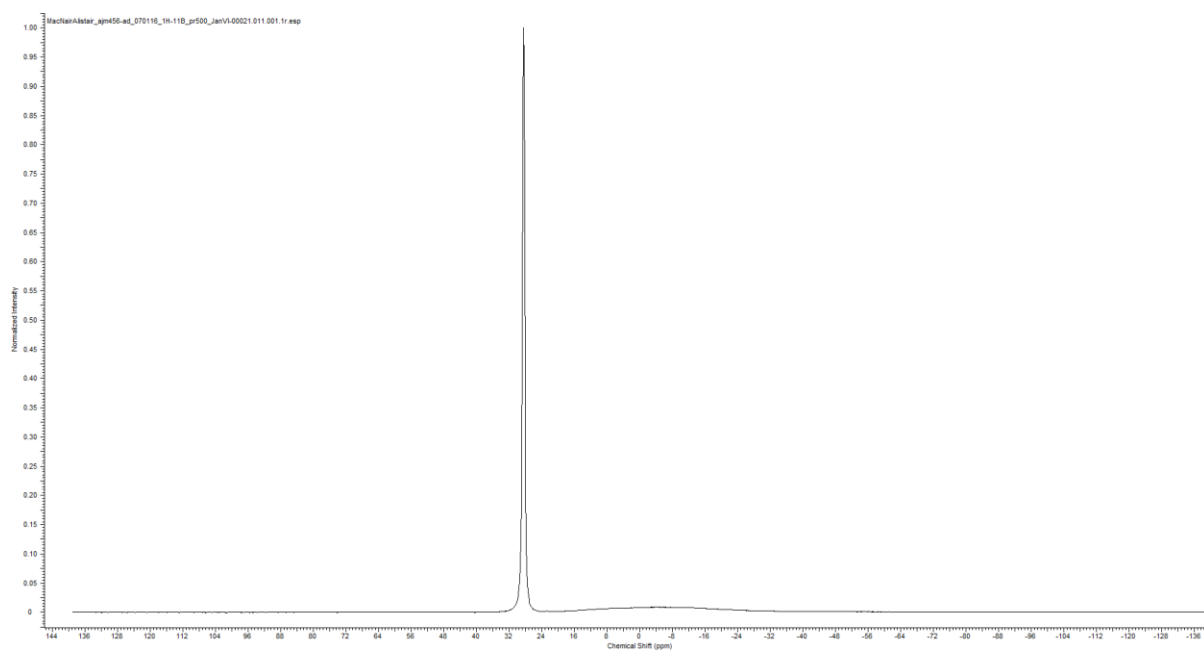
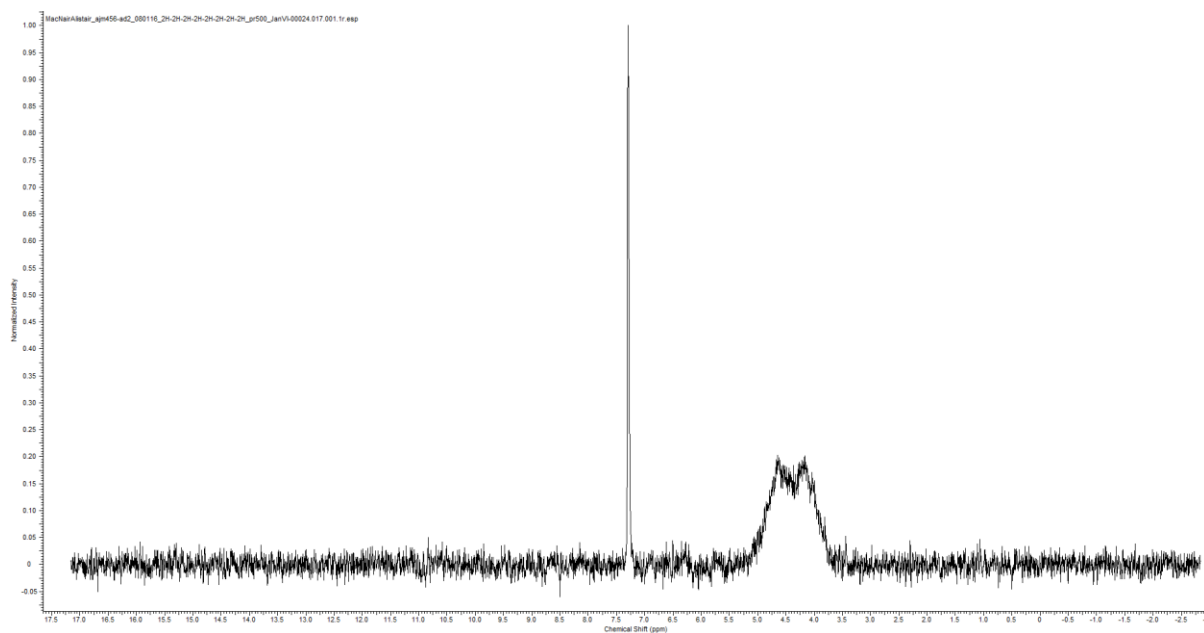


$^1\text{H}$ , 500 MHz,  $\text{C}_6\text{D}_6$



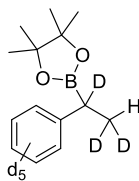
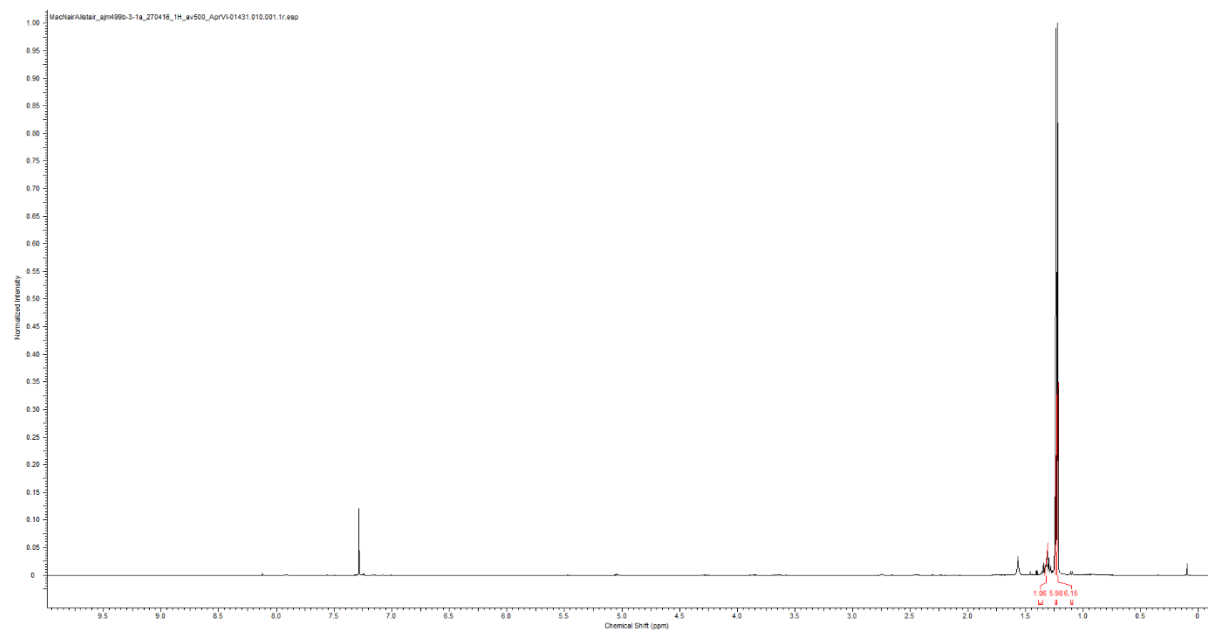
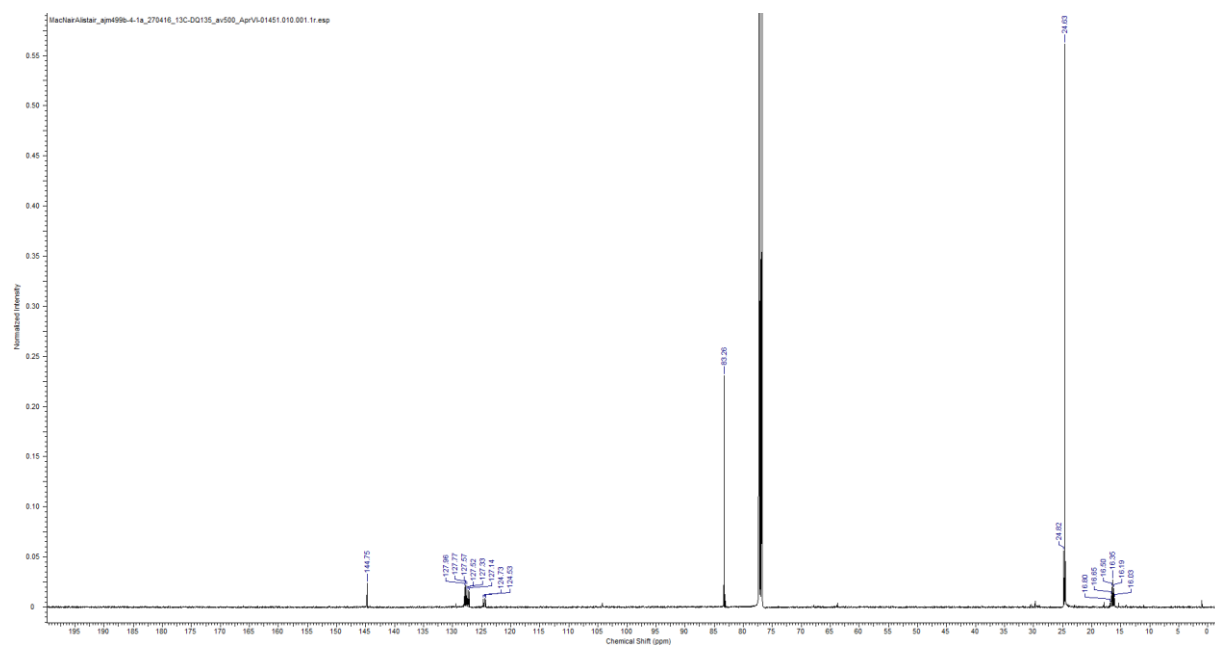
$^{13}\text{C}$ , 126 MHz,  $\text{C}_6\text{D}_6$



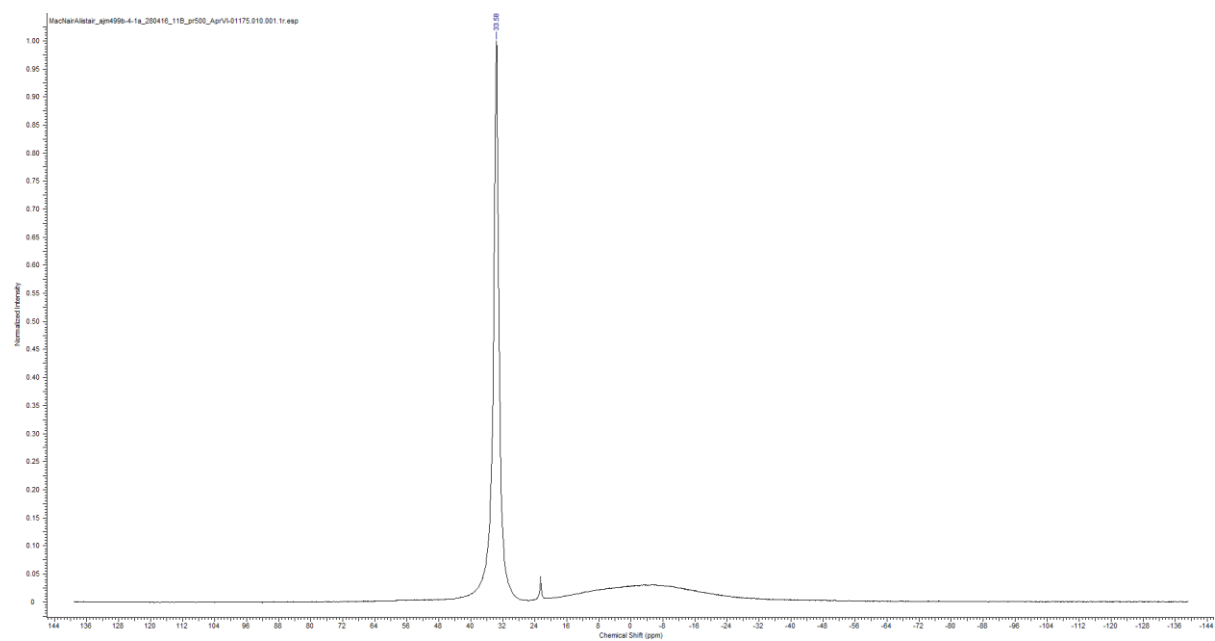
<sup>11</sup>B, 160 MHz, C<sub>6</sub>D<sub>6</sub> $^2\text{D}$ , 77 MHz,  $\text{C}_6\text{H}_6$ 



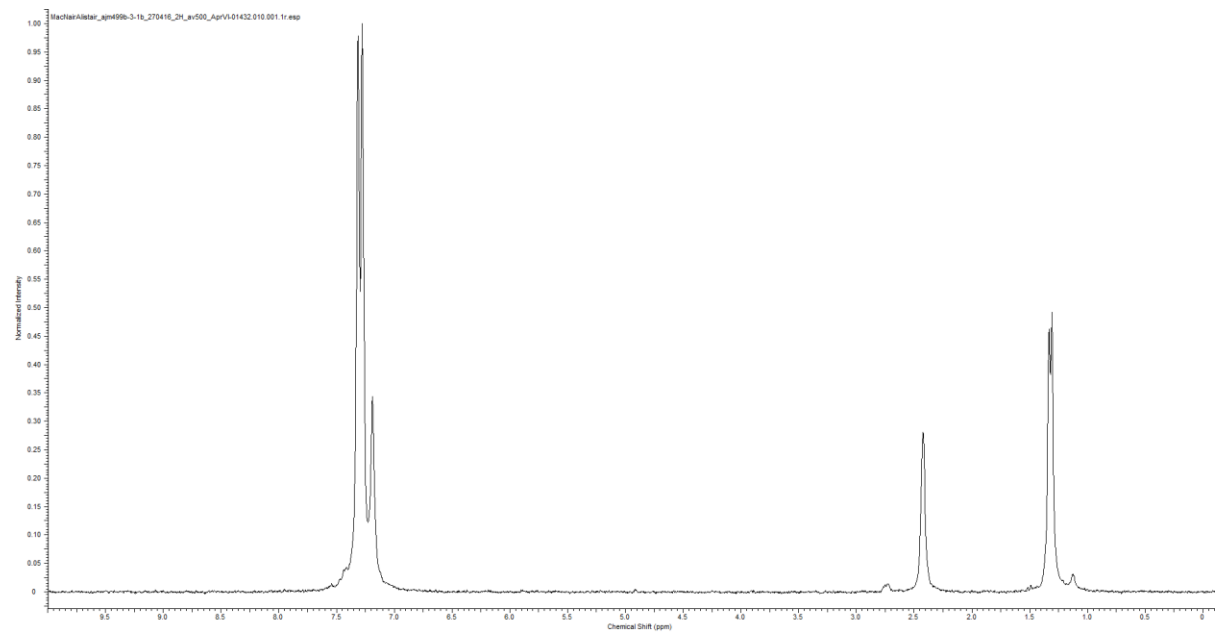
**2-[1-(*d*<sub>5</sub>-Phenyl)-1-*d*<sub>1</sub>-2-*d*<sub>2</sub>-ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*d*<sub>8</sub>-194)**

<sup>1</sup>H, 500 MHz, CDCl<sub>3</sub><sup>13</sup>C, 126 MHz, CDCl<sub>3</sub>

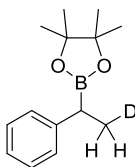
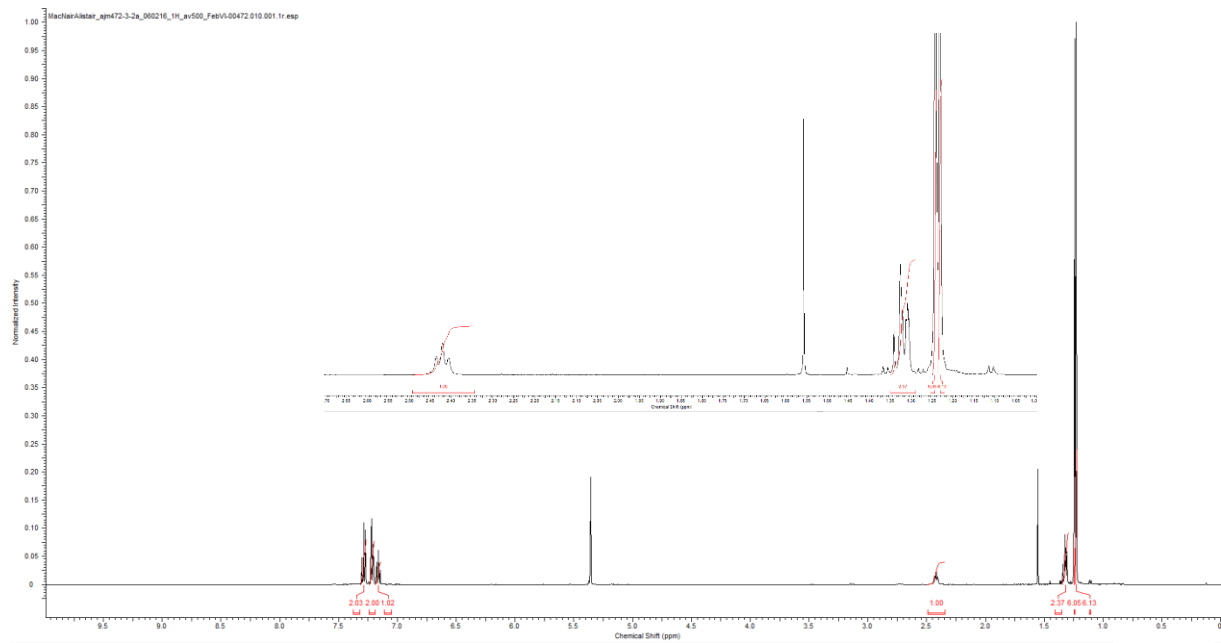
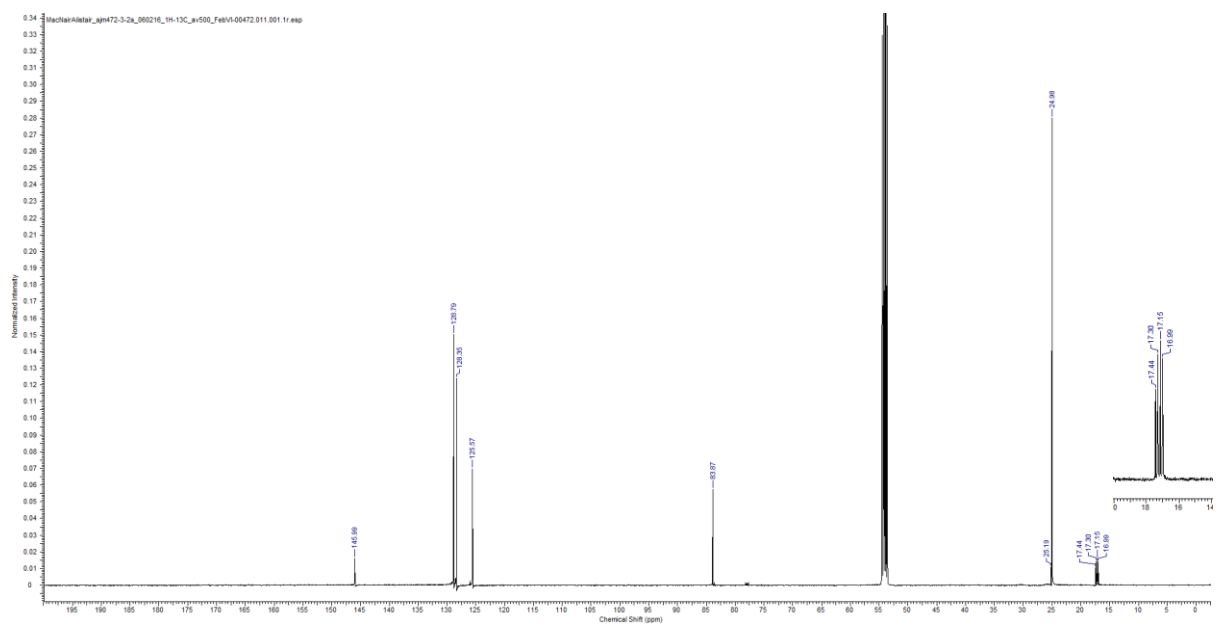
$^{11}\text{B}$ , 160 MHz,  $\text{CDCl}_3$



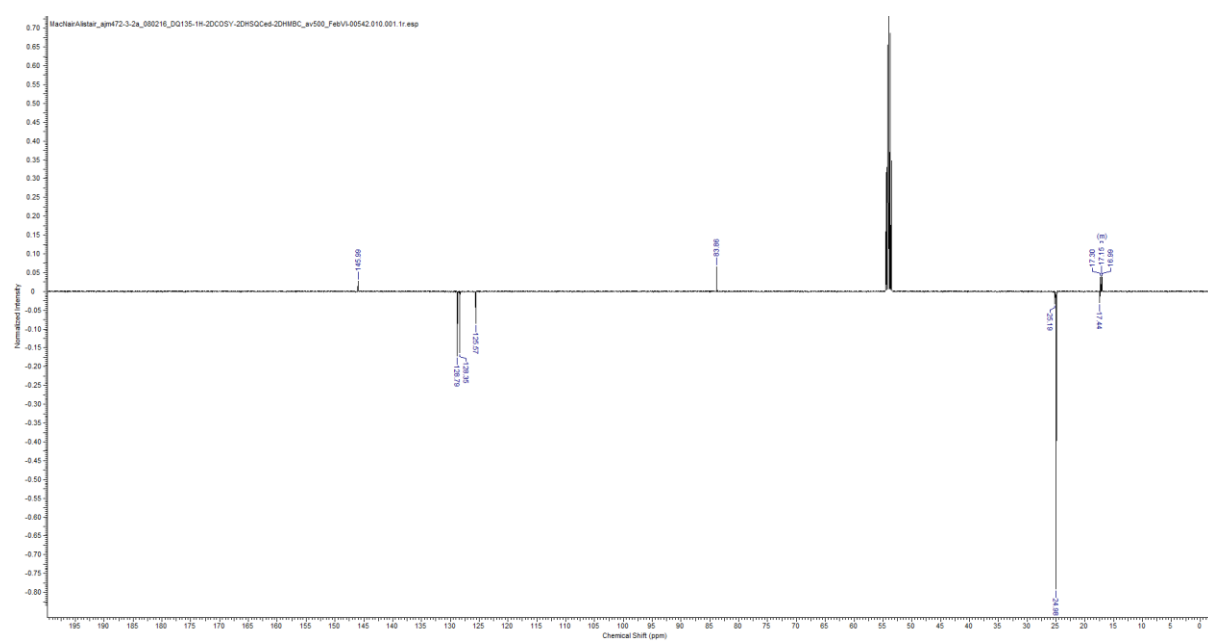
$^2\text{D}$ , 77 MHz,  $\text{CHCl}_3$



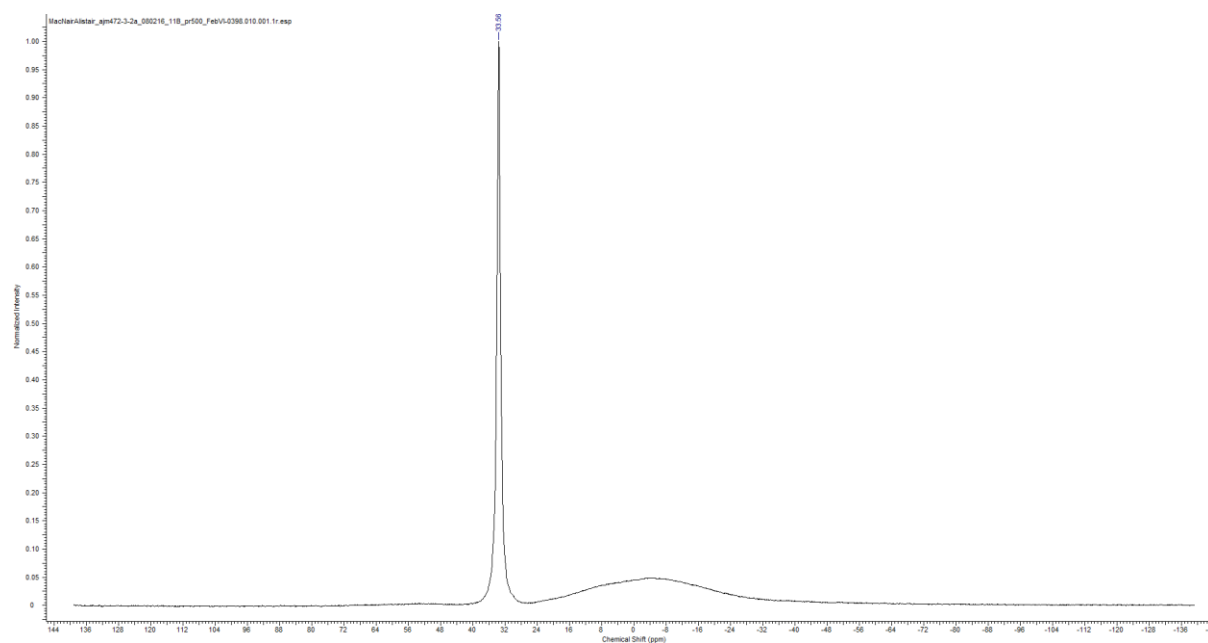
**2-(1-Phenyl-2-*d*<sub>1</sub>-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*d*<sub>1</sub>-194)**  
(Isolated as an approximately 3:1 mixture with the fully protonated species **194**)

 $^1\text{H}$ , 500 MHz,  $\text{CD}_2\text{Cl}_2$  $^{13}\text{C}$ , 126 MHz,  $\text{CD}_2\text{Cl}_2$ 

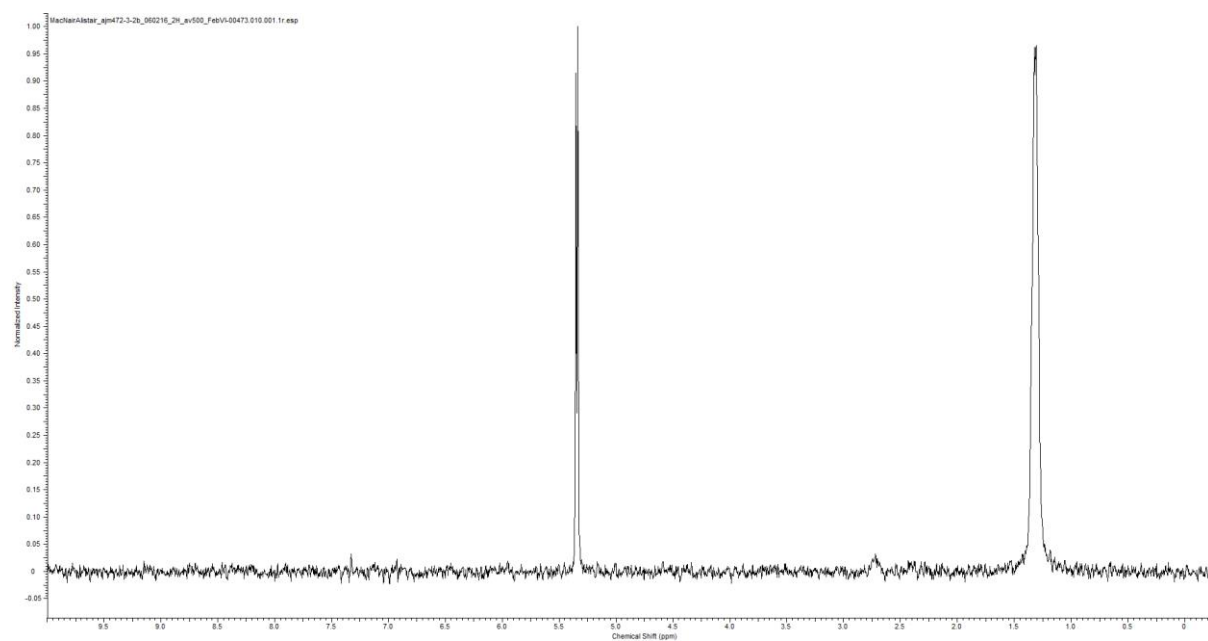
$^{13}\text{C}$  DEPT 135 (with quaternary) 126 MHz,  $\text{CD}_2\text{Cl}_2$



$^{11}\text{B}$ , 160 MHz,  $\text{CD}_2\text{Cl}_2$



$^2\text{D}$ , 77 MHz,  $\text{CH}_2\text{Cl}_2$



# checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.      CIF dictionary      Interpreting this report

## Datablock: se4002

---

Bond precision:	C-C = 0.0025 A	Wavelength=0.71073	
Cell:	a=24.0256(5)	b=13.1262(3)	c=22.3213(6)
	alpha=90	beta=90	gamma=90
Temperature:	120 K		
	Calculated	Reported	
Volume	7039.4(3)	7039.4(3)	
Space group	P b c n	P b c n	
Hall group	-P 2n 2ab	-P 2n 2ab	
Moiety formula	C36 H38 Fe N4 O2, C4 H8 O	C36 H38 Fe N4 O2, C4 H8 O	
Sum formula	C40 H46 Fe N4 O3	C40 H46 Fe N4 O3	
Mr	686.66	686.66	
Dx,g cm-3	1.296	1.296	
Z	8	8	
Mu (mm-1)	0.472	0.472	
F000	2912.0	2912.0	
F000'	2915.75		
h,k,lmax	34,19,32	34,18,31	
Nref	11393	10975	
Tmin,Tmax	0.875,0.971	0.909,0.984	
Tmin'	0.759		

Correction method= GAUSSIAN

Data completeness= 0.963      Theta(max)= 31.177

R(reflections)= 0.0460( 8858)      wR2(reflections)= 0.1099( 10975)

S = 1.080      Npar= Npar = 439

---

The following ALERTS were generated. Each ALERT has the format  
**test-name\_ALERT\_alert-type\_alert-level.**  
Click on the hyperlinks for more details of the test.

---



### Alert level C

PLAT220_ALERT_2_C	Large Non-Solvent	C	Ueq(max)/Ueq(min)	Range	3.1	Ratio
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### Alert level G

PLAT083_ALERT_2_G	SHELXL Second Parameter in WGHT	Unusually Large.	5.65	Why ?
PLAT232_ALERT_2_G	Hirshfeld Test Diff (M-X)	Fe22 -- C2 ..	6.9	su

- 0 **ALERT level A** = Most likely a serious problem - resolve or explain  
 0 **ALERT level B** = A potentially serious problem, consider carefully  
 1 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight  
 2 **ALERT level G** = General information/check it is not something unexpected
- 0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data  
 3 ALERT type 2 Indicator that the structure model may be wrong or deficient  
 0 ALERT type 3 Indicator that the structure quality may be low  
 0 ALERT type 4 Improvement, methodology, query or suggestion  
 0 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special\_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

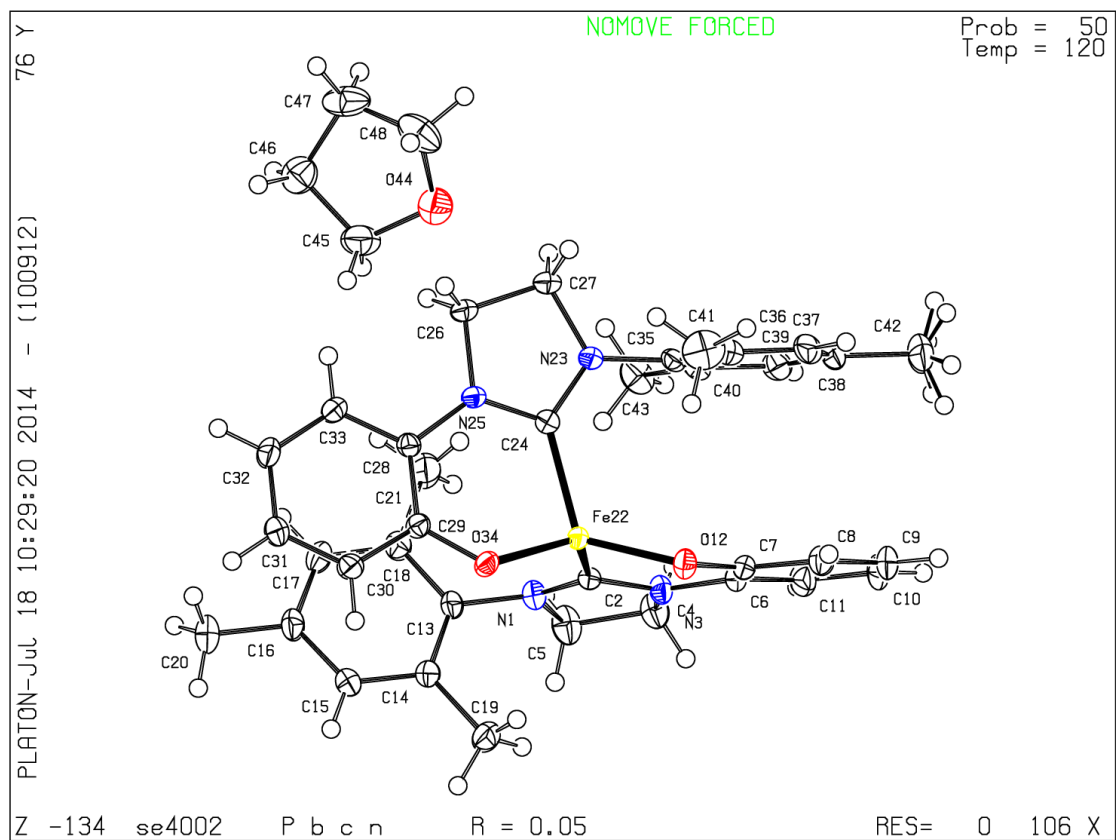
### Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

### Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

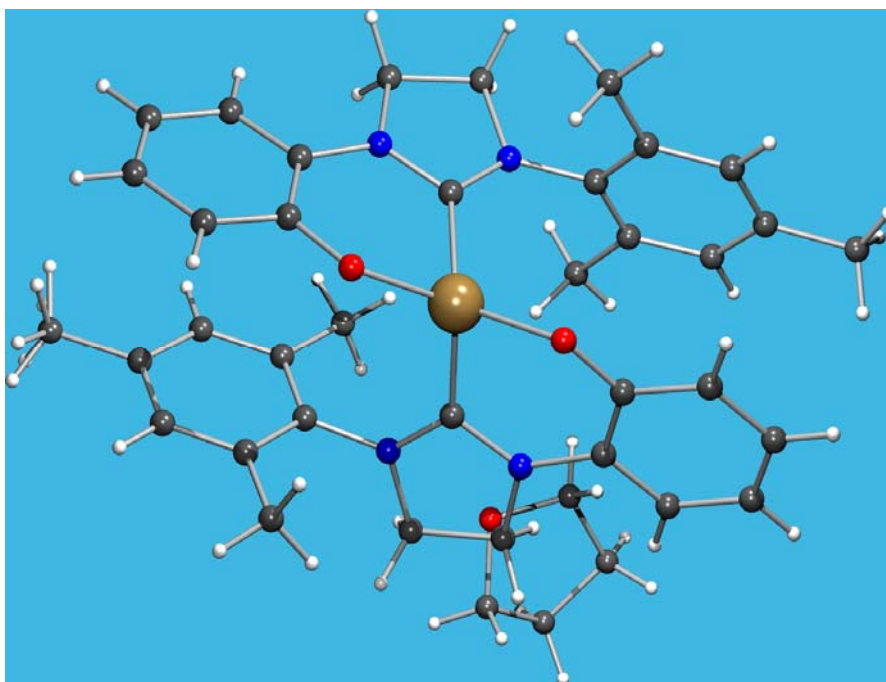
**PLATON version of 05/02/2014; check.def file version of 05/02/2014**





**Crystal Structure Service**  
School of Chemistry  
*The University of Edinburgh*

**Your code:** ajm278\_rc1    **Our code:** se4002



**Comment**

Compound ajm278\_rc1 was provided as large dark green multiple block crystals which, after separation, were suitable for single crystal X-ray diffraction, yielding structure se4002.

The asymmetric unit of se4002 is shown in Figure 1. The compound has crystallized as a THF solvate. One methyl group (bonded to C42) was modelled over two sites, rotated from each other by 60°, with each H atom given occupancy of 0.5.

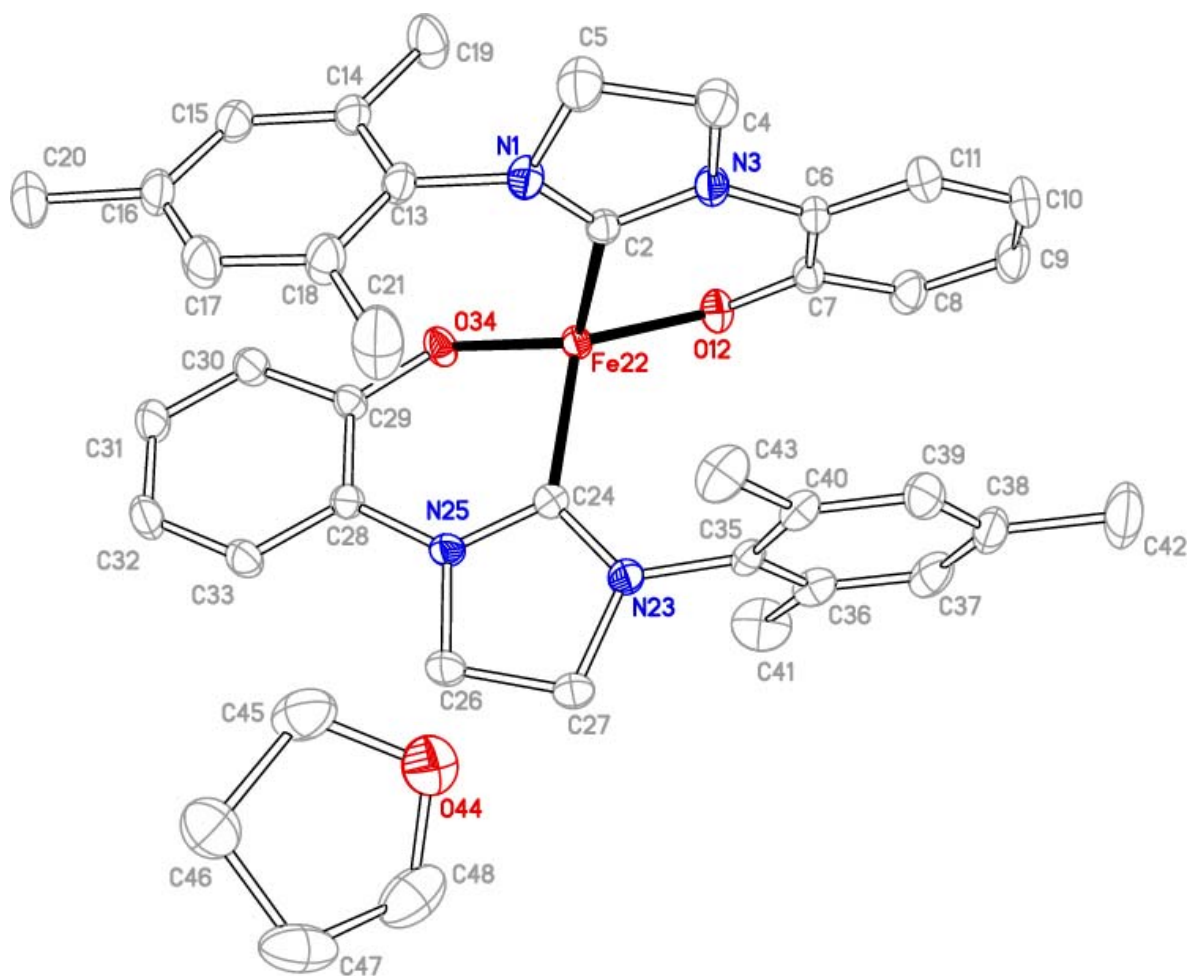


Figure 1. The asymmetric unit of se4002. Displacement ellipsoids are at the 50% probability level and H atoms are omitted.

### Acknowledgement:

We thank The University of Edinburgh for funding the diffractometer purchase.

### References:

**CRYSTALISPRO** (data collection, integration and absorption correction)  
Agilent Technologies, (2013), *CrysAlisPro*, Agilent Technologies UK Ltd, Yarnton, UK

**SHELXTL** (structure solution, refinement and graphics)  
Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.

**OLEX 2** (graphics)  
Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009).  
*J. Appl. Cryst.*, **42**, 339—341.

Table 1. Crystal data and structure refinement for se4002.

Identification code	se4002	
Empirical formula	C <sub>40</sub> H <sub>46</sub> Fe N <sub>4</sub> O <sub>3</sub>	
Formula weight	686.66	
Temperature	120.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P b c n	
Unit cell dimensions	a = 24.0256(5) Å	$\alpha = 90^\circ$ .
	b = 13.1262(3) Å	$\beta = 90^\circ$ .
	c = 22.3213(6) Å	$\gamma = 90^\circ$ .
Volume	7039.4(3) Å <sup>3</sup>	
Z	8	
Density (calculated)	1.296 Mg/m <sup>3</sup>	
Absorption coefficient	0.472 mm <sup>-1</sup>	
F(000)	2912	
Crystal size	0.5841 x 0.2354 x 0.0624 mm <sup>3</sup>	
Theta range for data collection	2.935 to 31.177°.	
Index ranges	-34 ≤ h ≤ 34, -18 ≤ k ≤ 17, -31 ≤ l ≤ 31	
Reflections collected	145241	
Independent reflections	10975 [R(int) = 0.0553]	
Completeness to theta = 25.242°	99.7 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.984 and 0.909	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	10975 / 0 / 439	
Goodness-of-fit on F <sup>2</sup>	1.080	
Final R indices [I > 2σ(I)]	R1 = 0.0460, wR2 = 0.1030	
R indices (all data)	R1 = 0.0631, wR2 = 0.1099	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.408 and -0.430 e.Å <sup>-3</sup>	

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for se4002.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U^{ij}$  tensor.

	x	y	z	U(eq)
Fe(22)	1684(1)	2390(1)	626(1)	16(1)
O(12)	1694(1)	1417(1)	-10(1)	22(1)
O(34)	2171(1)	2450(1)	1297(1)	22(1)
N(1)	526(1)	2492(1)	1206(1)	21(1)
N(3)	525(1)	1763(1)	329(1)	21(1)
N(23)	1751(1)	4384(1)	-91(1)	20(1)
N(25)	2081(1)	4519(1)	812(1)	18(1)
C(2)	851(1)	2201(1)	750(1)	18(1)
C(4)	-77(1)	1814(2)	488(1)	28(1)
C(5)	-61(1)	2188(2)	1134(1)	32(1)
C(6)	700(1)	1352(1)	-229(1)	20(1)
C(7)	1272(1)	1184(1)	-367(1)	20(1)
C(8)	1392(1)	733(1)	-922(1)	27(1)
C(9)	982(1)	471(1)	-1330(1)	33(1)
C(10)	431(1)	655(2)	-1196(1)	35(1)
C(11)	293(1)	1089(1)	-648(1)	28(1)
C(13)	744(1)	2796(1)	1779(1)	20(1)
C(14)	950(1)	2054(1)	2167(1)	22(1)
C(15)	1155(1)	2363(1)	2721(1)	24(1)
C(16)	1158(1)	3378(1)	2895(1)	25(1)
C(17)	948(1)	4096(1)	2499(1)	31(1)
C(18)	739(1)	3824(1)	1939(1)	28(1)
C(19)	962(1)	946(1)	1990(1)	35(1)
C(20)	1395(1)	3701(2)	3491(1)	35(1)
C(21)	522(1)	4628(2)	1516(1)	52(1)
C(24)	1845(1)	3872(1)	417(1)	17(1)
C(26)	2132(1)	5568(1)	572(1)	24(1)
C(27)	1935(1)	5458(1)	-71(1)	27(1)
C(28)	2257(1)	4289(1)	1405(1)	17(1)
C(29)	2293(1)	3271(1)	1620(1)	18(1)
C(30)	2486(1)	3134(1)	2206(1)	23(1)
C(31)	2640(1)	3940(1)	2571(1)	27(1)
C(32)	2603(1)	4925(1)	2355(1)	26(1)

C(33)	2415(1)	5096(1)	1776(1)	23(1)
C(35)	1527(1)	3943(1)	-626(1)	18(1)
C(36)	1887(1)	3539(1)	-1055(1)	22(1)
C(37)	1660(1)	3177(1)	-1585(1)	30(1)
C(38)	1092(1)	3180(1)	-1693(1)	29(1)
C(39)	744(1)	3563(1)	-1251(1)	26(1)
C(40)	953(1)	3956(1)	-718(1)	20(1)
C(41)	2503(1)	3456(2)	-939(1)	40(1)
C(42)	860(1)	2762(2)	-2273(1)	51(1)
C(43)	566(1)	4393(2)	-256(1)	32(1)
O(44)	1102(1)	7409(1)	481(1)	38(1)
C(45)	1030(1)	7504(2)	1110(1)	41(1)
C(46)	1175(1)	8589(2)	1287(1)	39(1)
C(47)	1337(1)	9090(2)	700(1)	44(1)
C(48)	1482(1)	8196(2)	306(1)	44(1)

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Table 3. Bond lengths [Å] and angles [°] for se4002.

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Fe(22)-O(12)	1.9098(11)
Fe(22)-O(34)	1.9017(11)
Fe(22)-C(2)	2.0341(16)
Fe(22)-C(24)	2.0385(15)
O(12)-C(7)	1.3253(19)
O(34)-C(29)	1.3301(18)
N(1)-C(2)	1.340(2)
N(1)-C(5)	1.474(2)
N(1)-C(13)	1.439(2)
N(3)-C(2)	1.3510(19)
N(3)-C(4)	1.489(2)
N(3)-C(6)	1.422(2)
N(23)-C(24)	1.337(2)
N(23)-C(27)	1.477(2)
N(23)-C(35)	1.431(2)
N(25)-C(24)	1.3493(19)
N(25)-C(26)	1.4825(19)
N(25)-C(28)	1.421(2)
C(4)-C(5)	1.525(3)
C(6)-C(7)	1.426(2)
C(6)-C(11)	1.395(2)
C(7)-C(8)	1.403(2)
C(8)-C(9)	1.385(3)
C(9)-C(10)	1.380(3)
C(10)-C(11)	1.389(3)
C(13)-C(14)	1.395(2)
C(13)-C(18)	1.396(2)
C(14)-C(15)	1.391(2)
C(14)-C(19)	1.507(2)
C(15)-C(16)	1.388(2)
C(16)-C(17)	1.388(3)
C(16)-C(20)	1.507(2)
C(17)-C(18)	1.394(3)
C(18)-C(21)	1.508(3)
C(26)-C(27)	1.519(2)
C(28)-C(29)	1.423(2)

C(28)-C(33)	1.398(2)
C(29)-C(30)	1.399(2)
C(30)-C(31)	1.384(2)
C(31)-C(32)	1.383(2)
C(32)-C(33)	1.388(2)
C(35)-C(36)	1.395(2)
C(35)-C(40)	1.396(2)
C(36)-C(37)	1.387(3)
C(36)-C(41)	1.506(3)
C(37)-C(38)	1.384(3)
C(38)-C(39)	1.387(3)
C(38)-C(42)	1.513(3)
C(39)-C(40)	1.390(2)
C(40)-C(43)	1.503(2)
O(44)-C(45)	1.422(3)
O(44)-C(48)	1.432(3)
C(45)-C(46)	1.518(3)
C(46)-C(47)	1.517(3)
C(47)-C(48)	1.508(3)

O(12)-Fe(22)-C(2)	91.80(5)
O(12)-Fe(22)-C(24)	117.71(6)
O(34)-Fe(22)-O(12)	127.25(5)
O(34)-Fe(22)-C(2)	120.25(6)
O(34)-Fe(22)-C(24)	91.38(5)
C(2)-Fe(22)-C(24)	109.53(6)
C(7)-O(12)-Fe(22)	126.33(10)
C(29)-O(34)-Fe(22)	126.65(9)
C(2)-N(1)-C(5)	113.46(13)
C(2)-N(1)-C(13)	122.90(13)
C(13)-N(1)-C(5)	121.31(13)
C(2)-N(3)-C(4)	112.30(13)
C(2)-N(3)-C(6)	126.74(13)
C(6)-N(3)-C(4)	120.82(13)
C(24)-N(23)-C(27)	113.80(13)
C(24)-N(23)-C(35)	124.53(13)
C(35)-N(23)-C(27)	121.55(13)
C(24)-N(25)-C(26)	112.46(13)

C(24)-N(25)-C(28)	126.93(13)
C(28)-N(25)-C(26)	120.58(12)
N(1)-C(2)-Fe(22)	129.91(11)
N(1)-C(2)-N(3)	108.10(13)
N(3)-C(2)-Fe(22)	121.93(11)
N(3)-C(4)-C(5)	102.42(13)
N(1)-C(5)-C(4)	102.34(14)
N(3)-C(6)-C(7)	122.24(14)
C(11)-C(6)-N(3)	118.27(15)
C(11)-C(6)-C(7)	119.48(15)
O(12)-C(7)-C(6)	124.82(14)
O(12)-C(7)-C(8)	118.18(15)
C(8)-C(7)-C(6)	117.00(15)
C(9)-C(8)-C(7)	122.65(17)
C(10)-C(9)-C(8)	119.75(17)
C(9)-C(10)-C(11)	119.46(17)
C(10)-C(11)-C(6)	121.64(17)
C(14)-C(13)-N(1)	119.18(14)
C(14)-C(13)-C(18)	121.30(15)
C(18)-C(13)-N(1)	119.51(15)
C(13)-C(14)-C(19)	121.22(15)
C(15)-C(14)-C(13)	118.31(15)
C(15)-C(14)-C(19)	120.45(15)
C(16)-C(15)-C(14)	122.02(16)
C(15)-C(16)-C(20)	121.22(17)
C(17)-C(16)-C(15)	118.16(16)
C(17)-C(16)-C(20)	120.61(16)
C(16)-C(17)-C(18)	121.92(16)
C(13)-C(18)-C(21)	121.31(16)
C(17)-C(18)-C(13)	118.28(16)
C(17)-C(18)-C(21)	120.41(16)
N(23)-C(24)-Fe(22)	129.97(11)
N(23)-C(24)-N(25)	108.04(13)
N(25)-C(24)-Fe(22)	122.00(11)
N(25)-C(26)-C(27)	103.17(12)
N(23)-C(27)-C(26)	102.22(12)
N(25)-C(28)-C(29)	122.15(13)
C(33)-C(28)-N(25)	118.19(13)



C(33)-C(28)-C(29)	119.63(14)
O(34)-C(29)-C(28)	124.32(14)
O(34)-C(29)-C(30)	118.46(13)
C(30)-C(29)-C(28)	117.20(14)
C(31)-C(30)-C(29)	122.67(15)
C(32)-C(31)-C(30)	119.54(16)
C(31)-C(32)-C(33)	119.77(15)
C(32)-C(33)-C(28)	121.20(15)
C(36)-C(35)-N(23)	119.63(14)
C(36)-C(35)-C(40)	121.00(15)
C(40)-C(35)-N(23)	119.33(14)
C(35)-C(36)-C(41)	121.14(16)
C(37)-C(36)-C(35)	118.26(15)
C(37)-C(36)-C(41)	120.55(16)
C(38)-C(37)-C(36)	122.25(16)
C(37)-C(38)-C(39)	118.16(16)
C(37)-C(38)-C(42)	120.70(19)
C(39)-C(38)-C(42)	121.13(19)
C(38)-C(39)-C(40)	121.70(16)
C(35)-C(40)-C(43)	120.95(15)
C(39)-C(40)-C(35)	118.59(15)
C(39)-C(40)-C(43)	120.46(15)
C(45)-O(44)-C(48)	106.38(16)
O(44)-C(45)-C(46)	108.20(17)
C(47)-C(46)-C(45)	103.93(18)
C(48)-C(47)-C(46)	103.03(17)
O(44)-C(48)-C(47)	104.83(16)

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for se4002. The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
Fe(22)	18(1)	14(1)	15(1)	0(1)	-2(1)	-1(1)
O(12)	23(1)	23(1)	19(1)	-5(1)	-2(1)	3(1)
O(34)	28(1)	15(1)	22(1)	-1(1)	-9(1)	1(1)
N(1)	21(1)	25(1)	17(1)	-3(1)	0(1)	1(1)
N(3)	20(1)	26(1)	16(1)	-2(1)	-2(1)	-2(1)
N(23)	27(1)	16(1)	18(1)	2(1)	-4(1)	-1(1)
N(25)	22(1)	14(1)	18(1)	2(1)	-2(1)	-1(1)
C(2)	23(1)	15(1)	15(1)	1(1)	-1(1)	0(1)
C(4)	19(1)	41(1)	24(1)	-3(1)	-1(1)	-2(1)
C(5)	22(1)	48(1)	26(1)	-6(1)	3(1)	-1(1)
C(6)	26(1)	20(1)	15(1)	-2(1)	-2(1)	-3(1)
C(7)	28(1)	16(1)	16(1)	-1(1)	-3(1)	-1(1)
C(8)	37(1)	24(1)	20(1)	-4(1)	2(1)	3(1)
C(9)	51(1)	30(1)	18(1)	-8(1)	-2(1)	-3(1)
C(10)	45(1)	39(1)	20(1)	-6(1)	-10(1)	-12(1)
C(11)	29(1)	34(1)	22(1)	-2(1)	-6(1)	-8(1)
C(13)	24(1)	22(1)	15(1)	-3(1)	2(1)	1(1)
C(14)	26(1)	20(1)	18(1)	-2(1)	2(1)	0(1)
C(15)	28(1)	25(1)	18(1)	1(1)	-1(1)	0(1)
C(16)	28(1)	30(1)	18(1)	-6(1)	2(1)	-1(1)
C(17)	45(1)	21(1)	26(1)	-8(1)	-1(1)	3(1)
C(18)	41(1)	22(1)	22(1)	-2(1)	-2(1)	6(1)
C(19)	56(1)	20(1)	30(1)	-2(1)	-12(1)	2(1)
C(20)	40(1)	39(1)	24(1)	-11(1)	-4(1)	-2(1)
C(21)	95(2)	24(1)	36(1)	-2(1)	-19(1)	16(1)
C(24)	15(1)	18(1)	17(1)	1(1)	0(1)	1(1)
C(26)	35(1)	15(1)	24(1)	3(1)	-5(1)	-2(1)
C(27)	41(1)	17(1)	23(1)	5(1)	-5(1)	-4(1)
C(28)	17(1)	18(1)	17(1)	1(1)	-2(1)	-1(1)
C(29)	17(1)	17(1)	20(1)	0(1)	-3(1)	0(1)
C(30)	27(1)	20(1)	22(1)	2(1)	-7(1)	-1(1)
C(31)	34(1)	27(1)	20(1)	0(1)	-9(1)	-2(1)
C(32)	33(1)	23(1)	23(1)	-6(1)	-7(1)	-2(1)

C(33)	29(1)	16(1)	24(1)	-1(1)	-4(1)	-2(1)
C(35)	22(1)	18(1)	14(1)	3(1)	0(1)	3(1)
C(36)	23(1)	21(1)	23(1)	2(1)	6(1)	5(1)
C(37)	44(1)	25(1)	19(1)	-1(1)	10(1)	7(1)
C(38)	48(1)	23(1)	17(1)	0(1)	-6(1)	1(1)
C(39)	26(1)	27(1)	26(1)	4(1)	-8(1)	1(1)
C(40)	22(1)	22(1)	17(1)	4(1)	2(1)	4(1)
C(41)	24(1)	44(1)	54(1)	-1(1)	10(1)	8(1)
C(42)	87(2)	40(1)	26(1)	-6(1)	-19(1)	1(1)
C(43)	27(1)	42(1)	28(1)	1(1)	7(1)	10(1)
O(44)	39(1)	38(1)	37(1)	-2(1)	-1(1)	1(1)
C(45)	54(1)	29(1)	40(1)	6(1)	14(1)	6(1)
C(46)	34(1)	39(1)	43(1)	-2(1)	-4(1)	-2(1)
C(47)	30(1)	39(1)	64(2)	20(1)	-10(1)	-10(1)
C(48)	31(1)	66(2)	37(1)	16(1)	4(1)	2(1)

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Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^{-3}$ ) for se4002.

	x	y	z	U(eq)
H(4A)	-255	1136	458	33
H(4B)	-278	2299	226	33
H(5A)	-314	2774	1194	38
H(5B)	-162	1638	1417	38
H(8)	1770	602	-1022	32
H(9)	1080	165	-1701	39
H(10)	148	487	-1476	42
H(11)	-87	1209	-556	34
H(15)	1297	1864	2988	28
H(17)	945	4794	2613	37
H(19A)	605	759	1809	53
H(19B)	1027	526	2347	53
H(19C)	1262	833	1701	53
H(20A)	1477	3095	3732	52
H(20B)	1123	4126	3702	52
H(20C)	1737	4090	3426	52
H(21A)	757	4655	1159	77
H(21B)	527	5293	1717	77
H(21C)	139	4460	1400	77
H(26A)	2522	5809	589	29
H(26B)	1892	6048	797	29
H(27A)	1624	5929	-160	32
H(27B)	2242	5584	-358	32
H(30)	2511	2462	2361	28
H(31)	2770	3816	2966	32
H(32)	2706	5483	2603	32
H(33)	2393	5775	1630	28
H(37)	1902	2918	-1885	35
H(39)	353	3557	-1315	32
H(41A)	2575	2872	-676	61
H(41B)	2635	4080	-745	61
H(41C)	2699	3361	-1319	61

H(42A)	482	3023	-2334	76
H(42B)	850	2016	-2253	76
H(42C)	1097	2976	-2607	76
H(42D)	1137	2320	-2463	76
H(42E)	769	3327	-2543	76
H(42F)	522	2368	-2189	76
H(43A)	638	5124	-212	48
H(43B)	628	4052	129	48
H(43C)	180	4289	-383	48
H(45A)	1276	7018	1322	49
H(45B)	640	7352	1221	49
H(46A)	851	8936	1470	46
H(46B)	1489	8600	1575	46
H(47A)	1023	9485	532	53
H(47B)	1661	9547	754	53
H(48A)	1433	8371	-122	53
H(48B)	1871	7979	373	53

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Table 6. Torsion angles [°] for se4002.

Fe(22)-O(12)-C(7)-C(6)	-21.7(2)
Fe(22)-O(12)-C(7)-C(8)	158.71(12)
Fe(22)-O(34)-C(29)-C(28)	-24.8(2)
Fe(22)-O(34)-C(29)-C(30)	157.04(12)
O(12)-C(7)-C(8)-C(9)	-179.28(16)
O(34)-C(29)-C(30)-C(31)	177.93(16)
N(1)-C(13)-C(14)-C(15)	-179.55(14)
N(1)-C(13)-C(14)-C(19)	1.6(2)
N(1)-C(13)-C(18)-C(17)	179.39(16)
N(1)-C(13)-C(18)-C(21)	-1.4(3)
N(3)-C(4)-C(5)-N(1)	11.08(18)
N(3)-C(6)-C(7)-O(12)	-2.3(2)
N(3)-C(6)-C(7)-C(8)	177.27(14)
N(3)-C(6)-C(11)-C(10)	-178.09(16)
N(23)-C(35)-C(36)-C(37)	-175.87(14)
N(23)-C(35)-C(36)-C(41)	6.6(2)
N(23)-C(35)-C(40)-C(39)	177.28(14)
N(23)-C(35)-C(40)-C(43)	-2.1(2)
N(25)-C(26)-C(27)-N(23)	5.13(17)
N(25)-C(28)-C(29)-O(34)	0.2(2)
N(25)-C(28)-C(29)-C(30)	178.35(14)
N(25)-C(28)-C(33)-C(32)	-178.48(15)
C(2)-N(1)-C(5)-C(4)	-10.1(2)
C(2)-N(1)-C(13)-C(14)	-74.2(2)
C(2)-N(1)-C(13)-C(18)	106.50(19)
C(2)-N(3)-C(4)-C(5)	-9.91(19)
C(2)-N(3)-C(6)-C(7)	12.0(2)
C(2)-N(3)-C(6)-C(11)	-169.27(16)
C(4)-N(3)-C(2)-Fe(22)	-173.44(11)
C(4)-N(3)-C(2)-N(1)	4.00(18)
C(4)-N(3)-C(6)-C(7)	-172.68(15)
C(4)-N(3)-C(6)-C(11)	6.1(2)
C(5)-N(1)-C(2)-Fe(22)	-178.61(13)
C(5)-N(1)-C(2)-N(3)	4.22(19)
C(5)-N(1)-C(13)-C(14)	87.3(2)
C(5)-N(1)-C(13)-C(18)	-91.9(2)

C(6)-N(3)-C(2)-Fe(22)	2.3(2)
C(6)-N(3)-C(2)-N(1)	179.70(14)
C(6)-N(3)-C(4)-C(5)	174.11(15)
C(6)-C(7)-C(8)-C(9)	1.1(2)
C(7)-C(6)-C(11)-C(10)	0.7(3)
C(7)-C(8)-C(9)-C(10)	0.1(3)
C(8)-C(9)-C(10)-C(11)	-0.9(3)
C(9)-C(10)-C(11)-C(6)	0.5(3)
C(11)-C(6)-C(7)-O(12)	178.93(15)
C(11)-C(6)-C(7)-C(8)	-1.5(2)
C(13)-N(1)-C(2)-Fe(22)	-15.7(2)
C(13)-N(1)-C(2)-N(3)	167.09(14)
C(13)-N(1)-C(5)-C(4)	-173.27(14)
C(13)-C(14)-C(15)-C(16)	0.1(3)
C(14)-C(13)-C(18)-C(17)	0.1(3)
C(14)-C(13)-C(18)-C(21)	179.3(2)
C(14)-C(15)-C(16)-C(17)	0.2(3)
C(14)-C(15)-C(16)-C(20)	-178.57(17)
C(15)-C(16)-C(17)-C(18)	-0.4(3)
C(16)-C(17)-C(18)-C(13)	0.2(3)
C(16)-C(17)-C(18)-C(21)	-179.0(2)
C(18)-C(13)-C(14)-C(15)	-0.3(3)
C(18)-C(13)-C(14)-C(19)	-179.16(18)
C(19)-C(14)-C(15)-C(16)	178.99(17)
C(20)-C(16)-C(17)-C(18)	178.41(18)
C(24)-N(23)-C(27)-C(26)	-4.05(19)
C(24)-N(23)-C(35)-C(36)	-90.54(19)
C(24)-N(23)-C(35)-C(40)	91.68(19)
C(24)-N(25)-C(26)-C(27)	-5.21(18)
C(24)-N(25)-C(28)-C(29)	11.6(2)
C(24)-N(25)-C(28)-C(33)	-170.43(15)
C(26)-N(25)-C(24)-Fe(22)	-177.02(11)
C(26)-N(25)-C(24)-N(23)	2.85(18)
C(26)-N(25)-C(28)-C(29)	-170.44(14)
C(26)-N(25)-C(28)-C(33)	7.5(2)
C(27)-N(23)-C(24)-Fe(22)	-179.21(12)
C(27)-N(23)-C(24)-N(25)	0.94(18)
C(27)-N(23)-C(35)-C(36)	85.24(19)

C(27)-N(23)-C(35)-C(40)	-92.54(19)
C(28)-N(25)-C(24)-Fe(22)	1.1(2)
C(28)-N(25)-C(24)-N(23)	-179.07(14)
C(28)-N(25)-C(26)-C(27)	176.57(14)
C(28)-C(29)-C(30)-C(31)	-0.4(2)
C(29)-C(28)-C(33)-C(32)	-0.5(2)
C(29)-C(30)-C(31)-C(32)	0.3(3)
C(30)-C(31)-C(32)-C(33)	-0.4(3)
C(31)-C(32)-C(33)-C(28)	0.4(3)
C(33)-C(28)-C(29)-O(34)	-177.76(15)
C(33)-C(28)-C(29)-C(30)	0.4(2)
C(35)-N(23)-C(24)-Fe(22)	-3.1(2)
C(35)-N(23)-C(24)-N(25)	177.01(14)
C(35)-N(23)-C(27)-C(26)	179.75(14)
C(35)-C(36)-C(37)-C(38)	-1.7(3)
C(36)-C(35)-C(40)-C(39)	-0.5(2)
C(36)-C(35)-C(40)-C(43)	-179.87(15)
C(36)-C(37)-C(38)-C(39)	0.1(3)
C(36)-C(37)-C(38)-C(42)	-178.95(17)
C(37)-C(38)-C(39)-C(40)	1.4(3)
C(38)-C(39)-C(40)-C(35)	-1.2(2)
C(38)-C(39)-C(40)-C(43)	178.21(16)
C(40)-C(35)-C(36)-C(37)	1.9(2)
C(40)-C(35)-C(36)-C(41)	-175.61(16)
C(41)-C(36)-C(37)-C(38)	175.78(17)
C(42)-C(38)-C(39)-C(40)	-179.56(17)
O(44)-C(45)-C(46)-C(47)	-0.2(2)
C(45)-O(44)-C(48)-C(47)	-36.5(2)
C(45)-C(46)-C(47)-C(48)	-20.9(2)
C(46)-C(47)-C(48)-O(44)	35.3(2)
C(48)-O(44)-C(45)-C(46)	22.8(2)

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Symmetry transformations used to generate equivalent atoms:



Table 7. Hydrogen bonds for se4002 [ $\text{\AA}$  and  $^\circ$ ].

D-H...A	d(D-H)	d(H...A)	d(D...A)	$\angle(\text{DHA})$
C(4)-H(4B)...O(44)#1	0.99	2.56	3.431(2)	146.9
C(26)-H(26A)...O(12)#2	0.99	2.45	3.301(2)	144.4
C(33)-H(33)...O(34)#2	0.95	2.55	3.4177(19)	152.4

Symmetry transformations used to generate equivalent atoms:

#1  $-x, -y+1, -z$  #2  $-x+1/2, y+1/2, z$

